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## ORIGINAL ARTICLES

# CHEMOTHERAPEUTIC ASPECTS OF STUDIES ON BACTERIAL VIRUSES

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MY GREAT pleasure in addressing this body stems in no small part from the fact that this occasion is almost the first indication I have had in 10 years that others besides my immediate chiefs at the Children's Hospital know why I am in a Department of Pediatrics. As many of you are aware, I am a biochemist. It is apparently a surprise to others of my profession that infectious disease is a problem of concern to both pediatricians and biochemists. This attitude, reflecting a tacit belief that the job of a biochemist is to study some esoteric compound, its origin or its fate, rather than chemical aspects of a clearly defined biologic problem is widely prevalent and can be a serious deterrent to the solution of many important medical problems. This is true in the sense that this view affects the general problem of uniting theoretic and practical work. I recall attending the dedication of a virology laboratory last year in which the guest speaker paid tribute to the contributions of research scientists who solved problems in the process of satisfying their intellectual curiosity, as well as to contributions of the research physician who undertook to solve the more practical aspects of the control of disease. It did not seem to have occurred to the speaker that a research scientist might be interested in doing more than titillating his neurones. And of course, in many instances, the speaker was unfortunately correct, since practicality is often viewed as only the unworthy illegitimate child of science, rather than merely as its natural offspring.

It has been said that The Children's Hospital Research Department, of which I am a member, is a fine place if you like viruses. However, the fact of the matter is that we do not know how to treat virus diseases any better than anyone else. I am not speaking of epidemiologic or diagnostic studies, or those on prevention, but rather what one does with

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a patient when he enters the hospital with a recognized disease entity. As is well known, we do not now have satisfactory antiviral agents. What I wish to discuss today are some bases on which such agents may be developed.

I came to The Children's Hospital during the war to work on the typhus vaccine. At the conclusion of those studies, I proposed to undertake a fundamental biochemical study of how viruses multiply in cells believing that such information might suggest methods of controlling virus multiplication. The notion that the metabolism of a virus-infected cell was interesting was totally unexplored at that time; and in order to facilitate the work,

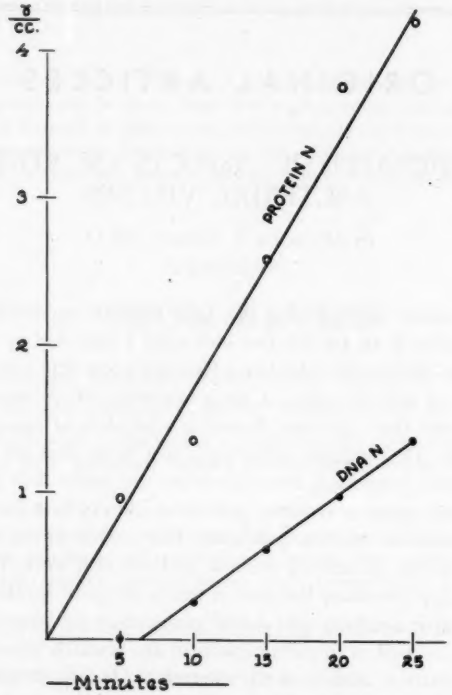


FIG. 1. Synthesis of protein and deoxyribonucleic acid (DNA) in T2r$^+$-infected E. coli. Ordinate presents increments over initial values.

a system particularly favorable in the technical sense was selected for study. This consisted of a bacterial host, Escherichia coli, and several bacterial viruses, notably the T2, T4 and T6 viruses.

The development of methods and first principles can often be facilitated by stripping a biologic problem down to its bare essentials, in this case homogeneous cell suspensions infected with virus in a rigorously controlled environment. The complete solution of our practical problem, the chemotherapy of human disease, cannot be attained solely by work at this level, but in my opinion neither can this level of work be ignored. Fortunately for my story, it is the position of our institution, its leadership and its personnel that we shall pursue practical biologic problems with an eye to their solution and that

if the theoretic bases for the solutions are not available, we shall attempt to uncover them.

At one time, as recently as 10 years ago, an important hypothesis on virus multiplication stated that a host cell contained large precursor molecules which in the presence of virus were transformed to more virus. If this theory had proved correct, it would have had important implications for chemotherapy, since the conversion of precursor to virus would require few steps involving the specificity of large molecules. We have no experience or skill in inhibiting reactions of this type. As a corollary of this hypothesis, it would also be predicted that gross synthesis would be slight or nonexistent and we began by testing this point.[1]

In the bacterial virus systems I have mentioned, the T-even viruses adsorb to the host and stop the normal growth and multiplication of the bacteria. After an interval termed the latent period, during which virus multiplication occurs within the infected cells, the cells break down or lyse to liberate newly formed virus. During the latent period, at a time when cell division had stopped, we discovered that synthesis continued at a considerable rate, as can be seen in Fig. 1. The rate of incorporation of newly absorbed nitrogen

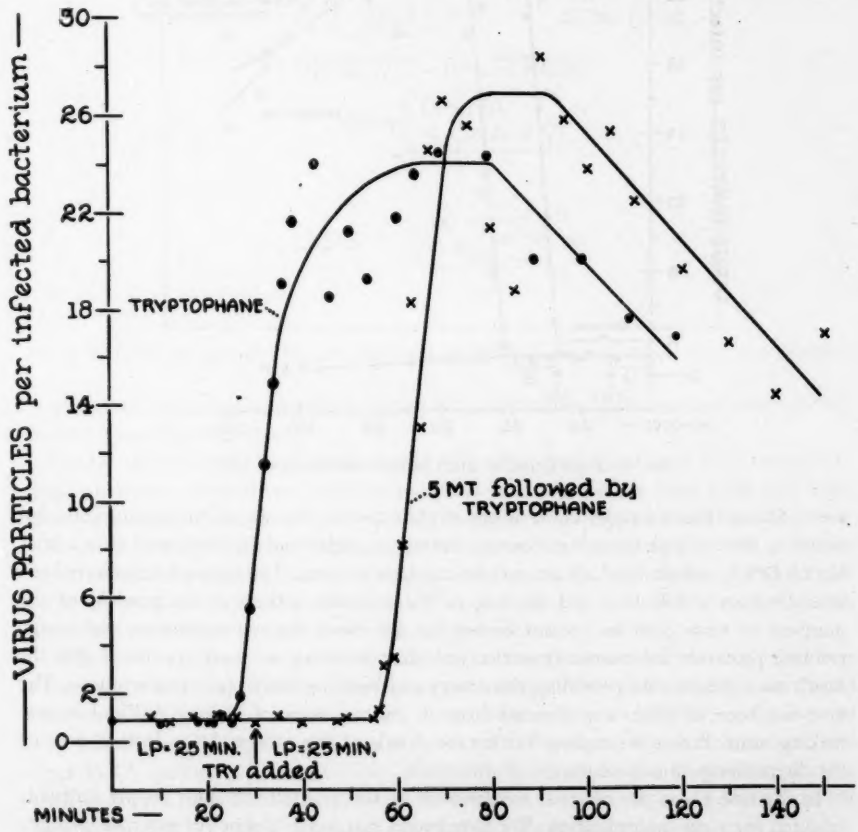


FIG. 2. Inhibition of T2r⁺ growth in E. coli in lactate media by 5-methyl tryptophan (5MT) at infection and reversal of inhibition by tryptophan. LP = latent period.

into newly formed protein was of the same order of magnitude as that in the uninfected cell, as was the rate of incorporation of phosphorus into newly synthesized nucleic acid.[1] It has been shown that much, if not all, of this synthesis is of virus constituents and that this material may be largely isolated in virus. That is—these viruses are largely built up *de novo* and do not require the transformation of large host precursor molecules to virus.

Furthermore, in Fig. 1, it can be seen that the synthesis of the virus constituents, protein and deoxyribosenucleic acid (DNA) as well as the intracellular formation of intact

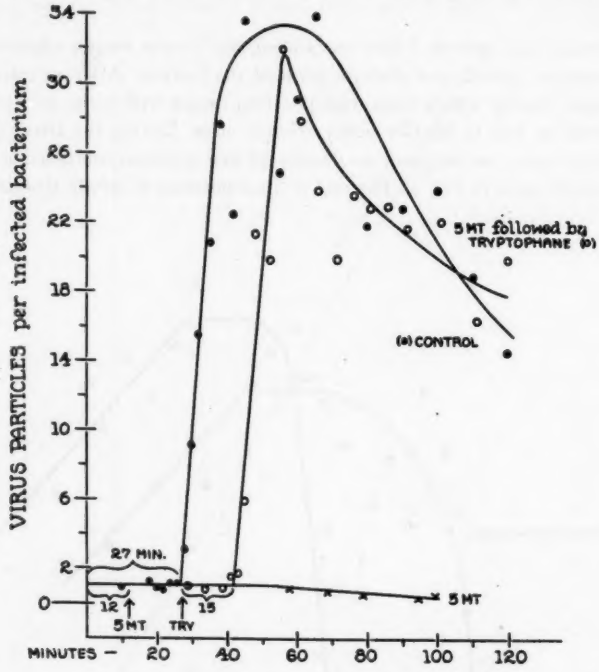


FIG. 3. Resumption of latent period interrupted by 5MT.

virus, do not fall on a single curve as one might expect in the case of multiplying cells, but rather on three independent linear curves. Protein is synthesized first, followed after a brief lag by DNA, and finished off several minutes later as virus. The virus particles have been assembled on a belt line, and the rate of the assembly process is independent of the numbers of virus particles present within the cell. Since the cell respiration and energy yielding processes are essentially unchanged after infection, we have concluded that the host's own enzymes are providing the energy and building blocks for virus synthesis. The host has been in some way diverted from its normal work of making cell and is now making virus. Before we explore further the details of this process, let us look at some of the chemotherapeutic consequences of this result.

In the first place, the external environment of the infected cell must supply nutrients essential for virus multiplication. We have found that in the absence of external nitrogen or carbon sources, for instance, virus synthesis does not occur. In our bacterial virus

system, the host can transform $(NH_4)_2SO_4$ and glucose into amino acids which form the virus protein. This process involves hundreds of steps, many of which can be readily inhibited. As one example of this, let us look at the incorporation of tryptophan into virus. Analogues of tryptophan are known, such as 5-methyl tryptophan, which competitively inhibit the incorporation of tryptophan into peptides. In Fig. 2, we are following virus liberation from infected bacteria in the presence and absence of 5-methyl tryptophan. When infection is begun in the presence of the antimetabolite, virus is not liberated. If tryptophan is then added to the inhibited system, virus multiplication begins and after exactly the normal latent period, virus is liberated.[2]

The control of virus synthesis by antimetabolites can be shown even more elegantly in Fig. 3. In this experiment, we will start virus synthesis off normally. After 10 minutes, 5-methyl tryptophan is added to interrupt multiplication. After a suitable interval, we

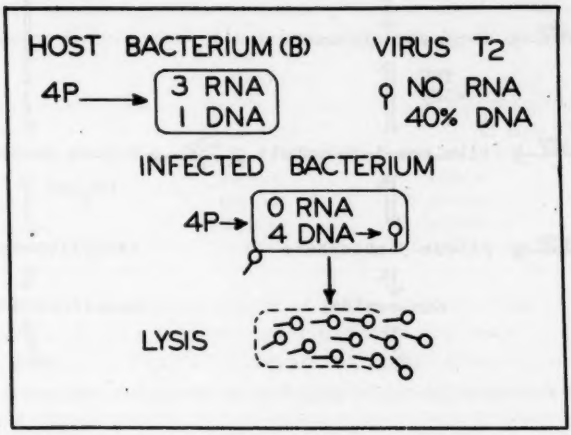


FIG. 4. Shunt in phosphorus (P) utilization and nucleic acid synthesis during virus multiplication.

start multiplication again by adding tryptophan, and following the residual latent period, normal virus liberation occurs.

Similar relations have been demonstrated with other amino acids and their antagonists. Some analogous observations in the amino acid series have recently been made with influenza virus and poliomyelitis virus systems. Competitive inhibitions resulting in the prevention of virus multiplication have been demonstrated in the metabolism and utilization of other small molecules such as vitamins and the nucleic acid bases in a variety of bacterial, plant, and animal virus systems. This promising result follows necessarily from the principle of *de novo* synthesis of virus described above.

When we examine phosphorus metabolism in normal and infected cells, some very interesting relations appear.[3] In normal growing bacteria, 80% of the cell P is distributed between ribose nucleic acids, RNA, and deoxyribose nucleic acid, DNA, in the ratio of 3 to 5 RNA to 1 DNA. On infection, as presented in Fig. 4, the P is entirely shunted into virus DNA synthesis, RNA synthesis being entirely stopped. The P which appears in virus is derived mainly from the external medium, but a small amount is derived from the host nuclear DNA which disintegrates immediately after infection.

It is possible to block the virus DNA synthesis by several methods, and one of the

most effective is to infect with an incomplete or damaged virus particle. For instance, ultraviolet irradiation is absorbed in the DNA and probably produces a structural alteration in this substance. When a virus particle carrying such an altered DNA moiety is used to infect a cell, we have found that both DNA and RNA synthesis are prevented although protein synthesis and the synthesis of purines and pyrimidines continue. On the other hand, the inhibition of protein synthesis by antimetabolites concomitantly prevents DNA synthesis.

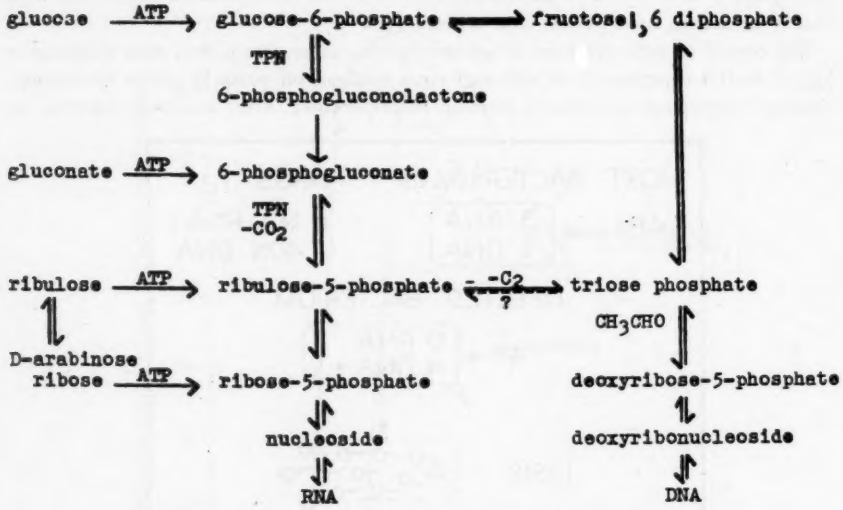


FIG. 5. Pathways of carbohydrate metabolism and nucleic acid synthesis in E. coli.

However, if we wish to control the distribution of P between the two nucleic acids, we must know more about the origin of ribose and deoxyribose phosphates in which the P is deposited. Over the past 4 years, we have demonstrated the existence in the host cells, E. coli, of two alternative pathways for glucose metabolism, as presented in Fig. 5. It appears quite probable that both pathways also exist in mammalian tissues as well as in many other organisms. One of these, which we call the phosphogluconate pathway, supplies the ribose phosphate for RNA, the other the triose phosphate which forms part of the deoxyribose phosphate incorporated into DNA. In our studies, we have discovered some four new enzymes associated with the phosphogluconate pathway, demonstrated the in vitro formation of ribose, and characterized other of the enzymes of this pathway. By means of isotope experiments, it was shown that the ribose RNA really is derived from this pathway during growth and that virus infection switches glucose metabolism into the deoxyribose pathway. Glucose-6-phosphate is the switch point leading from a common precursor to both pathways.

As yet, we do not know of compounds besides virus which can produce this shunt from one system to another. We are certain such compounds do exist and are looking precisely for such controlling compounds at the present time. It is possible that the metabolic pattern of tumor cells may also be ascribed to the relative dominance of one of these paths

over the other. For instance, in tumor formation, adult cells which have stopped making DNA may now be induced to make this substance.

However, we do know that certain compounds such as gluconate or the pentoses can only be used via the phosphogluconate pathway and that these carbon sources are not very satisfactory for virus multiplication.[4] Thus by feeding these substances, instead of glucose to host cells, we can limit their ability to synthesize DNA and virus.

The fact that infected cells make DNA when offered carbon sources which can be used only via the phosphogluconate pathway signifies that the virus does not inhibit the use of the pathway during glucose metabolism. The virus does not directly inhibit the enzymes of carbohydrate metabolism leading to RNA synthesis even though the use of these enzymes is affected. Where does the controlling mechanism lie? We hope that we now have the answer to this problem.

Until this point, we have found that the building blocks involved in virus synthesis are qualitatively the same as those involved in normal cell growth. Virologists have expressed

TABLE 1

| E. coli RNA | E. coli DNA | T2 Virus DNA |
|---|---|---|
| adenine | adenine | adenine |
| guanine | guanine | guanine |
| uracil | thymine | thymine |
| cytosine | cytosine | 5-hydroxymethyl cytosine |

the opinion that it would therefore be difficult, if not impossible, to inhibit virus synthesis selectively. Quite recently, as a result of analytic studies on virus nucleic acid carried out in collaboration with Dr. G. Wyatt of the Department of Agriculture of Canada, we have found that the virus contains a pyrimidine not found in the host nucleic acid nor indeed found as yet in any other organism. This is the first evidence for a qualitatively new building block in a virus as contrasted to the host. The virus lacks a pyrimidine which is present in the host, and evidence is available that some of the host pyrimidine is converted to virus pyrimidine. The new pyrimidine has been rigorously identified as 5-hydroxymethyl cytosine.[5] In table 1 are summarized the bases of host and virus nucleic acid.

The existence of this new compound suggests why the host is now diverted to make virus. If the host were unable to make or utilize cytosine, it could no longer make its own RNA and DNA, nor possibly any of the structures associated with these nucleic acids. Instead, the formation of hydroxymethyl cytosine might compel the synthesis of virus DNA rather than host nucleic acid, diverting the metabolism of P, for instance, to virus DNA and nitrogen to protein associated with the DNA to form virus.

In Fig. 6 are indicated some of the possible biochemical interrelations of the pyrimidines. Very little is known of their origin and metabolism in the cell; we have quite a complex series of reactions which are possible. The new pyrimidine can be seen to be a formaldehyde addition compound of cytosine. One key problem that arises is whether the new pyrimidine is a normal intermediate or one which arises only in virus infection. Related to this is the question of whether the enzyme that effects this synthesis is present in host or in virus.

It is not yet known whether animal viruses also contain this compound, nor whether we may now be able to block virus synthesis specifically by preventing its formation.

However, all of these are distinct possibilities which require investigation at the present time.

The very existence of this new pyrimidine containing a hydroxymethyl group has opened up new possibilities in the problem of methyl group formation. As you know, both folic acid and vitamin $B_{12}$ have been implicated in methyl group synthesis, but it has been impossible at present to subdivide the problem further and to assign a specific role to each of these vitamins. For the first time, we now may have an orderly sequence of compounds and reactions for the dissection of this question.

It is known that the shotgun approach which has prevailed for the last decade, of routinely testing every conceivable compound in the chemotherapy of virus diseases, has

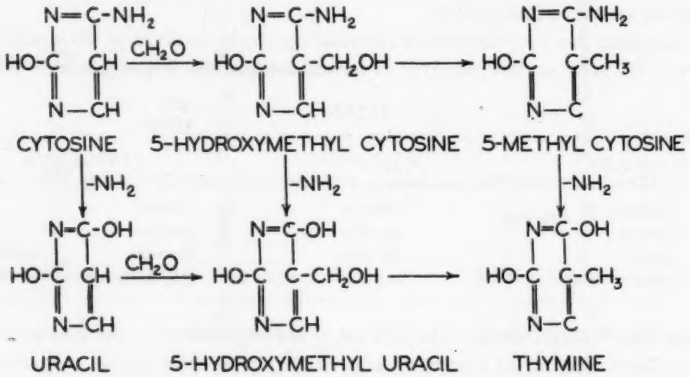


FIG. 6. Possible interrelationships of biochemically known pyrimidines.

been exceedingly expensive and has been fruitless to date. In the past year, I have been enormously heartened to see that certain pharmaceutical houses have decided to try a rational approach to this problem. The above examples illustrate that the rational investigation of the processes of virus synthesis does tell us which areas of metabolism should be particularly susceptible to a chemotherapeutic approach. However, we cannot extrapolate blindly from the bacterial viruses to other systems and we do lack such basic information for more complex systems, despite the fact that the methodology of study devised on the bacterial viruses is quite practicable for animal virus systems. There can be no denying the fact that the obtaining of such information will be a difficult and very expensive matter, but it is my conviction that the necessary fund of knowledge can be so obtained.

## ACKNOWLEDGMENT

In the course of these studies over about six years, I have had many collaborators without whose efforts many of the points covered would not have been discovered. I take great pleasure in acknowledging the contributions of Dr. Dwight B. McNair Scott, Dr. L. L. Weed, Mrs. Lorraine Roth, Mrs. Ruth Raff, Miss Catherine Fowler and Miss Rachel Arbogast.

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# A HITHERTO UNRECOGNIZED BIOCHEMICAL DIFFERENCE BETWEEN HUMAN MILK AND COW'S MILK

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THE starting point of these investigations, a preliminary report of which is presented herewith, has been one of the basic problems of pediatric research: human milk versus cow's milk.

Infants fed human milk in sufficient quantity distinguish themselves from those receiving cow's milk by their generally higher resistance to infections, including not only intestinal but also respiratory disorders.[1-3] The question whether this beneficial effect is due to breast feeding or to human milk as such has not received intensive critical analysis in the recent literature.

The intestinal flora of a normal breast-fed infant is characterized by the prevalence of Lactobacillus bifidus[4, 5] in contrast to the mixed flora of infants fed cow's milk formulae. The fecal pH is distinctly acid in breast-fed infants and is shifted toward the neutral or even alkaline range in infants fed cow's milk.

Attempts to relate these differences to the different chemical composition of human and cow's milk were only partially successful. The use of dilute cow's milk formulae with added carbohydrate up to more elaborate adaptations of cow's milk to human milk were based on this principle. However, all have been of rather moderate dimensions, in accordance with the present knowledge of the chemical composition of human and cow's milk. The known chemical differences between human and cow's milk, although in several respects significant, are even when most pronounced within the same order of magnitude.†

During the past three years the author's effort was directed toward the study of the metabolic requirements of L. bifidus as isolated from the stools of breast-fed and bottle-fed infants.[6] It was possible to devise a semisynthetic medium on which L. bifidus could be maintained indefinitely, at least for several years, without loss of its major morphologic, metabolic and serologic qualities. The composition of the medium is summarized in table 1. The atmosphere consists of nitrogen (90%) and $CO_2$ (10%).

In the course of these investigations the author encountered an apparently specfic mutant of L. bifidus which at primary isolation has shown only scant or no growth on the original medium. Further propagation of this strain, which was named L. bifidus var. Penn, was achieved in consecutive subcultures when human milk was added to the medium. With increased supplements of human milk to the original liquid medium acid production increased gradually toward a maximum (Fig. 1). In contrast, cow's milk

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* In collaboration with Richard Kuhn, Ph.D., R. F. Norris, M.D., C. S. Rose, Ph.D., A. Gauhe, Ph.D., J. R. E. Hoover, M.A., H. W. Ruelius, Ph.D., G. F. Springer, M.D., and F. Zilliken, Ph.D.

† In this connection we disregard the presence of lipase and lysozyme in human milk.

TABLE 1

MEDIUM FOR L. BIFIDUS

| | (per liter) |
|---|---|
| Lactose | 35 gm. |
| Sodium acetate (anhydrous) | 25 gm. |
| Casein hydrolysate (NZ case, Sheffield) | 5 gm. |
| Alanine, cystine, tryptophane | 200 mg. each |
| Asparagine | 100 mg. |
| Adenine, guanine, xanthine, uracil | 10 mg. each |
| $KH_2PO_4$ | 5 gm. |
| $MgSO_4 \cdot 7H_2O$ | 200 mg. |
| $FeSO_4 \cdot 7H_2O$ | 10 mg. |
| NaCl | 10 mg. |
| $MnSO_4 \cdot 2H_2O$ | 7 mg. |
| Vitamins: | |
| Thiamine · HCl | 200 γ |
| Riboflavin | 200 γ |
| Calcium pantothenate | 400 γ |
| Pyridoxine · HCl | 1200 γ |
| p-Aminobenzoic acid | 10 γ |
| Folic acid | 10 γ |
| Biotin | 4 γ |
| Ascorbic acid (added after autoclaving) | 1 gm. |

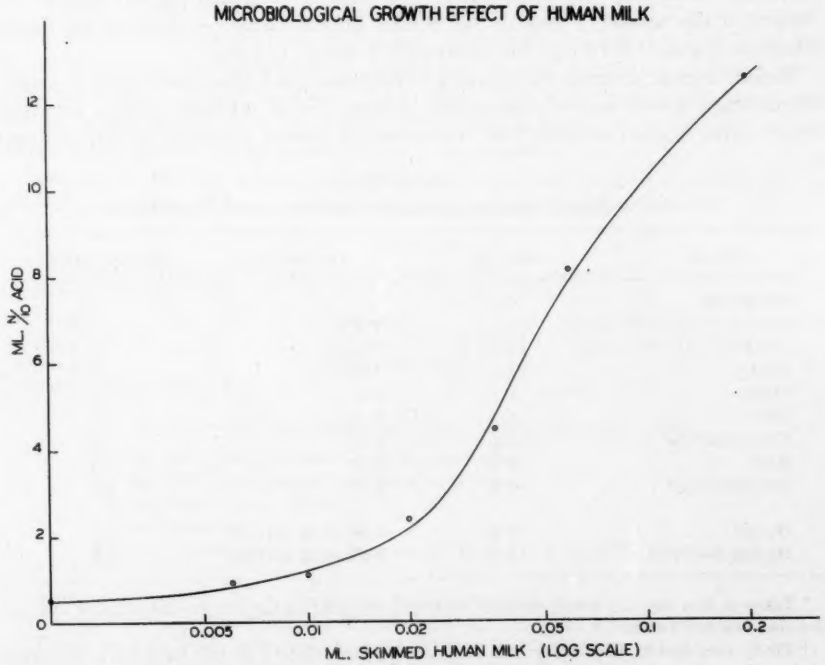


FIG. 1. Growth was measured by production of acid in 40 hr. old cultures (titrated with N/10 NaOH).

TABLE 2

ASSAY OF HUMAN AND COW'S MILK

| Supplement (per 10 cc. medium) | | Titration after 40 hr. (cc. N/10 NaOH) |
|---|---|---|
| None | | 0.4 |
| Human milk (skimmed) | 0.02 cc. | 2.2 |
| | 0.06 | 7.9 |
| | 0.2 | 12.5 |
| Cow's milk (skimmed) | 0.1 cc. | 0.6 |
| | 0.3 | 0.8 |
| | 1.0 | 2.3 |

was practically inactive (table 2). By selecting as arbitrary unit 0.06 cc. human milk/10 cc. of the liquid medium, the comparative figures of acid production indicate a ratio of activity of about 1:40 from cow's milk to human milk. Thus, with regard to this microbiologic growth factor, the activity of cow's milk moves in a definitely lower order of magnitude than that of human milk.

In further studies the activity of human milk was compared with that of the milk of other species (table 3). The average relative activity was highest for human colostrum, closely followed by rat colostrum, then by human milk, rat milk and cow's colostrum. All the other milks tested, in particular the milk from ruminants, such as cows, sheep and goats, has shown only very slight activity. The milk of the guinea pig was inactive. Expressed in dry residue, 1 unit of the Bifidus growth factor is contained for human colostrum in about 1.5-2.5 mg., for human milk in about 5 to 6 mg.

Various organic compounds, especially carbohydrates and many others such as various microbiologic growth factors, yeast extract, peptone, several vegetable extracts, not represented in the original medium, have been tested for growth promoting activity and have

TABLE 3

ACTIVITY OF HUMAN MILK AS COMPARED WITH MILK FROM OTHER SPECIES

| Species | Activity | One unit in | Relative Activity |
|---|---|---|---|
| Guinea pig | 0 | — | — |
| Cow | (+) | 2.5 cc. | 2.5 |
| Sheep | (+) | 2.5 cc. | 2.5 |
| Goat | (+) | 2.5 cc. | 2.5 |
| Mare | + | 0.5 | 12 |
| Sow | + | 0.4 | 15 |
| Cow colostrum* | ++ | 0.15 | 40 |
| Rat† | ++ | 0.13 | 45 |
| Rat colostrum† | ++ | 0.03 | 200 |
| Human | ++ | 0.06 (0.02 to 0.15) | 100 |
| Human colostrum | ++ | 0.02 (0.01 to 0.03) | 300 |

* Taken on first day; cow's milk obtained on fourth day after parturition was only slightly more active than late cow's milk.

† Kindly furnished by Dr. Luckey from Professor Reynier's Germ Free Life Laboratory, University of Notre Dame.

TABLE 4

DISTRIBUTION OF BIFIDUS FACTOR IN MAN

| | |
|---|---|
| Colostrum | 0.01 to 0.03 cc. (average 0.02 cc.) |
| Milk | 0.02 to 0.15 cc. (average 0.06 cc.) |
| Uterine mucus (10%) | 0.02 cc. |
| Ovarian cyst fluid (10%) pseudomucinous | 0.02 cc. |
| Meconium (10% suspension) | 0.05 cc. |
| Semen | 0.07 cc. |
| Gastric juice | 0.45 cc. |
| Saliva | 0.03 to 3.0 cc. (average 0.5 cc.) |
| Urine | 0.1 to 1.0 cc. |
| Tears | 1.0 cc. |
| Amniotic fluid | 1.0 cc. |

been found ineffective. Very slight activity was exhibited by liver compounds. Wilson liver fraction B was active only with 60 mg. as the unit, Difco Bacto-Liver with 250 mg., compared with human colostrum and milk effective with 1.5-6 mg. as unit. A purified liver extract (Parke Davis) was ineffective in doses up to 5 cc.

With regard to the distribution of the Bifidus growth factor in man table 4 contains a selection of pertinent data.

It is of special interest that colostrum has been found considerably richer in the microbiologic growth factors than late milk. The fact that gastric juice has been found just as active in cases[6] of pernicious anemia than in normal persons excludes the possibility that the "Bifidus factor" might be identical with Castle's intrinsic factor. The high activity of meconium, semen, gastric juice, ovarian cyst, amniotic fluid and tears in addition to that of colostrum and milk appears to be reminiscent of the distribution of blood group polysaccharides in human secretions. Saliva from cow, bull's semen and testes were practically inert as sources of the growth factor, whereas gastric mucin from hog, a well known source of blood group substance A, was very effective.

Comparative data on nitrogen-containing polysaccharides (muco-polysaccharides) as possible source of the Bifidus growth factor are summarized in table 5.

TABLE 5

NITROGEN-CONTAINING POLYSACCHARIDES SHOWING NO OR ALMOST NO L. BIFIDUS ACTIVITY

| | | |
|---|---|---|
| α-Heparin | Ovomucoid | Polysaccharides from pneumococci |
| β-Heparin* | Hyaluronic acid (K salt)‡ | types I, II, III, XIV§ |
| Ovomucin | Chondroitin sulfate | |
| Urinary mucopolysaccharide† | | |

Nitrogen-containing polysaccharides with high activity for L. bifidus

0.6 mg. Blood group substance A (Sharp and Dohme)
0.5 mg. Blood group substance B (Sharp and Dohme)
0.6 mg. Gastric mucin (Wilson)
5 mg. Meconium
4-10 mg. Polysaccharides from Pneumococci Types IV, V, VI, VIII, XVIII, XIX§

* Generously donated by Dr. A. Winterstein, Basle, Switzerland.
† Kindly furnished by Drs. Tamm and Horsfall, Rockefeller Institute of Medical Research.
‡ Kindly given by Dr. J. Seifter and Dr. R. W. Whitley, Wyeth Institute, Philadelphia.
§ Kindly furnished by Dr. Colin M. MacLeod, New York University, New York City.

Whereas the activity of purified blood group substance A and B, of gastric mucin, or of meconium was found to be nondialyzable, the Bifidus growth factor of human milk is present in a large proportion in a dialyzable form. The curves represented in figure 2 give the rate of dialyzability for the milk factor in human milk compared with the rate of dialysis for glucose. lactose and a trisaccharide (melezitose). The shape of the curves seems to indicate that the milk factor in its dialyzable form must have a higher molecular size than even the trisaccharide tested. In addition to the dialyzable fraction a varying portion of the growth factor in human milk is present in a nondialyzable form.

During the course of these studies on the purification and isolation of the milk factor the interesting observation was made that ammonium salts in high concentration appeared

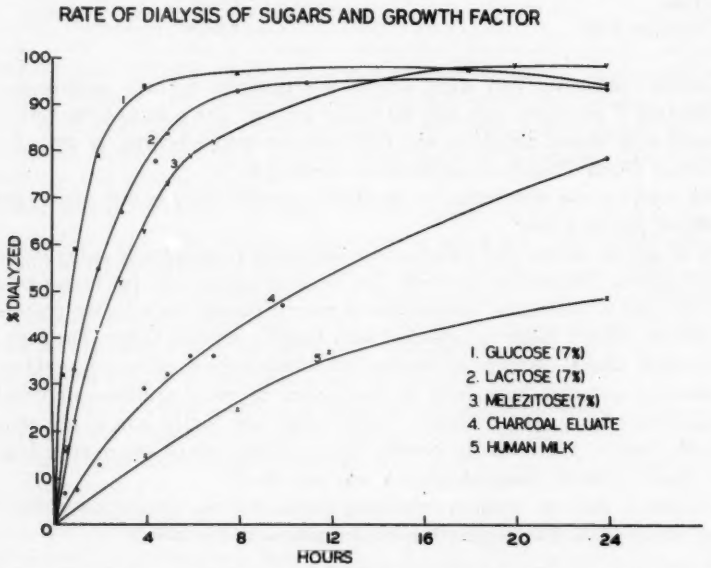


FIG. 2. "Charcoal eluate" represents active concentrate prepared from deproteinized human milk adsorbed on charcoal and eluted with acetic acid and phenol.
Microbiologic tests were carried out in dialysates and in dialysed residue (at end of experiment).

to have some growth-promoting activity, in all probability ammonium ion being a precursor of the real growth factor. Two milligrams of the $NH_4$ + ion have the activity of 1 unit independently if the ammonium ions are added as chloride, sulfate, phosphate, acetate, etc. In form of $(NH_4)_2SO_4$ the unit would represent 7.5 mg. of the salt. This would mean that approximately 15 gm. of $(NH_4)_2SO_4$ would have to be added to 100 cc. cow's milk in order to attain the same microbiologic activity for L. bifidus var. Penn as found in human milk. The relatively high activity of urine is due primarily to its ammonium content augmented after autoclaving through liberation of ammonium from urea. N-acetyl-glucosamine and N-acetyl-galactosamine, known constituents of blood group substance, exhibited more pronounced but, compared with human milk or colostrum, still definitely weak activity (2 to 3 mg./unit). Deproteinization of human milk furnished concentrates with higher activity. After adsorption of such concentrates on charcoal and elution with water and acetic acid, fractions were obtained which were free from lactose,

TABLE 6

ACTIVITY AND NITROGEN CONTENT OF PREPARATIONS, ACTING AS "GROWTH FACTOR" FOR L. BIFIDUS VAR. PENN

| Substance | mg./unit | % N | γ N/unit |
|---|---|---|---|
| Ammonium salts (expressed as $NH_4$+ion) | 2 | 77.8 | 1560 |
| N-acetyl-glucosamine | 2–3 | 5.86 | 120–180 |
| N-acetyl galactosamine | 2–3 | 5.86 | 120–180 |
| Blood group substance A | 0.6 | 2.9 | 17 |
| Blood group substance B | 0.6 | 3.0 | 17 |
| Mucin (Wilson) | 0.6 | 3.0 | 18 |
| Human milk, deprot., conc. | 2–3 | 0.77 | 17 |
| Charcoal eluates from human milk | 0.20–0.30 | 1.7–2.0 | 4–6 |

high in activity and which contained the unit in 200-300 γ. Table 6 contains comparative data on activity and nitrogen content of various preparations acting as growth factor for the special strain, the L. bifidus var. Penn.

Further, the intriguing and paradoxic observation was made that an enzyme preparation obtained from L. bifidus var. Penn requiring the milk factor for its growth may completely inactivate it when mixed in a test tube with a solution of the growth factor, either from human milk or from meconium. In contrast, no such enzyme was found in regular strains of L. bifidus growing in the semisynthetic basal medium without added milk factor (table 7). The enzymatic inactivation of the milk factor goes parallel in meconium with the loss of the blood-group titer and with liberation of a dialyzable reducing-substance, consisting chiefly of N-acetyl-d-glucosamine (table 8). Loss of one unit increases the amount of the dialyzable reducing substance by ca. 200 γ (expressed as glucose).

The chemical characteristics of highly active concentrates obtained from human milk and its breakdown products as determined after acid or enzymatic hydrolysis are summarized in table 9.

No similar compound and in particular no amino sugar-containing saccharide with similar properties was found, when cow's milk was worked up in exactly the same way.

Polonovski and Lespagnol stated that human milk contains, besides lactose, two other

TABLE 7

ENZYMATIC INACTIVATION OF "BIFIDUS GROWTH FACTOR"

| | Unit in |
|---|---|
| Human milk | 0.1 cc. |
| Human milk+specific Bifidus enzyme | 1.0 |
| Human milk+Bifidus enzyme boiled | 0.095 |
| Meconium 1% | 0.43 cc. |
| Meconium+specific Bifidus enzyme | no activity |
| Meconium+specific Bifidus enzyme (boiled) | 0.62 |
| Meconium 1% | 0.43 cc. |
| Meconium+enzyme from regular Bifidus strain | 0.43 |

TABLE 8

RATE OF ENZYMATIC INACTIVATION OF MECONIUM

| Time | Unit of growth factor | Reducing sugar mg./cc. |
|---|---|---|
| 0 | 0.6 | .15 |
| ½ hr. | 0.6 | .16 |
| 1 hr. | 0.62 | .17 |
| 2 hr. | 0.73 | .21 |
| 4 hr. | 0.8 | .23 |
| 8 hr. | 1.0 | .29 |
| 23 hr. | 1.4 | .33 |
| 40 hr. | 2.0 | .40 |

disaccharides to which the names "allolactose" and "gynolactose" have been given. In their last publication[6] they state that the levorotatory gynolactose preparations still contained saccharides of lower reducing power as well as small amounts of nitrogen. It is possible that these preparations contained the L. bifidus factor.

N-acetyl-d-glucosamine, L-fucose and D-galactose are the same chemical bricks from which in our body the giant molecules of the blood group substances are built up, with a molecular weight of about 260,000 (Morgan[8]). The blood group substances are non-dialyzable, they are quantitatively precipitated from water by alcohol at a concentration

TABLE 9

CHEMICAL CHARACTERISTICS OF LACTOSE-FREE PREPARATIONS OF "L. BIFIDUS FACTOR" FROM HUMAN MILK

N = 1.6 to 2.0%, $[\alpha]_D^{25} = -10°$ to $-40°$ (in water), No. S, No. P.

| | |
|---|---|
| Crystallized products:* (after acid hydrolysis) | D-Glucosamine (Hydrochloride)<br>L-Fucose (Diphenylhydrazone)<br>D-Galactose (Mucic acid) |
| Enzymatic hydrolysis (by paper chromatography) | N-acetyl-glucosamine<br>Fucose<br>Galactose |

* Isolation and characterization by mixed melting points, analysis, etc., were done by Adeline Gauhe, Ph.D., at the Max-Planck Institute for Medical Research, Heidelberg.

between 50 to 60% and a large moiety of their molecules is built up from protein, which on hydrolysis yields different amino acids.

In contrast, the L. bifidus factor as obtained from human milk dialyzes easily, it is not precipitated by alcohol up to concentrations of more than 80% and it is free of any amino acids, peptides or protein-like substances (table 10). As one would expect from these facts the preparations of the dialyzable L. bifidus factor from human milk in serologic tests do not show any blood group substance activity at all.* It has been a theoretic extrapolation by Morgan,[8] that the protein-free part of the blood group substances will be made up of "repeating units" consisting of N-acetyl-d-hexosamine, L-fucose and d-galactose residues. It now appears that something like that is really found in nature: it is the L. bifidus factor as it comes from the mother's breast.

* Personal communication from Dr. Peter Dahr, Göttingen.

The abundance of L. bifidus factor furnished by every mother to her child is highly impressive; but also the fact that it is furnished in two different ways. In the meconium it is present as the high molecular form of the blood group substances. In the colostrum and later on in the breast milk there are lower molecular forms of the growth factor. This observation is made without prejudice concerning the specific role of this microbiologic growth factor in promoting the fecal L. bifidus flora in breast-fed infants.

Recently, Petuely and Kristen[9,10] have postulated the presence of a specific substance in human milk. responsible for the development of L. bifidus flora in the feces of breast-fed infants. According to these authors, their factor is characterized by distinct chemical lability and by the absence of any direct microbiologic growth effect on L. bifidus. They

TABLE 10

| Properties | Blood Group Substances | L. Bifidus Factor From Breast Milk |
|---|---|---|
| Amino acids | + | − |
| Dialysis | − | + |
| Precipitation by alcohol (50 to 60%) | + | − |

assumed that their factor must act indirectly through the intestinal mucosa. No chemical characteristics were given.

Twenty years ago, working on cow's milk, through the isolation of riboflavin, two fields of research came together which were completely separated up to that time: the field of vitamins and that of enzymes.

Today, working on human milk we recognize another bridge. This bridge connects the growth factors of micro-organisms with the blood group substances of our body and thus with the whole field of immunologic reactions.

It may be that coming research will broaden the first outlook into still other fields:

1. The distribution of L. bifidus factor in man resembles to some extent the frequency of cancer incidence for the corresponding tissues. Mammary glands, the stomach and sex organs are among the first in both cases. It might be anticipated that with malignant tumors growing in these organs the cellular metabolism of the nitrogen-containing saccharides would not remain unaffected.

2. It is known that human milk (Sabin[11]), saliva (Rose[12]) and other nitrogen-containing polysaccharides (Horsfall,[13,14] etc.) as well as derivatives of blood group polysaccharides (Burnet[15]) have a delaying effect on certain experimental virus infections. The hitherto unknown rather large content of nitrogen-containing saccharides (L. bifidus factor) in human milk might, therefore, possibly lead to a better understanding of the higher resistance of the breast-fed infant.

## Summary

A specific mutant of L. bifidus (var. Penn) isolated from the feces of a breast-fed infant has shown no growth in the usual medium satisfactory for most strains of L. bifidus. It required for its propagation the addition of a specific "growth factor" present in human milk. Cow's milk had only 1/30 to 1/100 of the activity of human milk. The average relative activity was highest for the human colostrum, closely followed by rat colostrum, then by human milk, rat milk and cow's colostrum (taken on the first day).

All the other milks tested, in particular the milk from ruminants such as sheep and goats in addition to cow's milk, have shown only very low activity. Sow's and mare's milk are slightly more active, guinea pig milk is inactive. This microbiologic growth factor is different from all known vitamins and growth factors. Very slight activity was exhibited by liver compounds, and practically none by yeast or meat. Meconium is highly active. Human semen, uterine (cervical) mucus, gastric juice (even in a case of pernicious anemia), saliva, amniotic fluid, and tears are also very active. The growth factor occurs in low and higher molecular form in human milk. In meconium it is present in undialyzable form. Purified blood group substance A and B are highly active. From human milk levorotatory active products were obtained containing N-acetyl glucosamine, fucose and galactose, but no amino acids. N-acetyl glucosamine and N-acetyl galactosamine were only slightly active.

L. bifiidus var. Penn contains a specific enzyme which inactivates the microbiologic growth factor required by the same strain. The enzymatic inactivation of meconium or purified blood group substance as growth factor is accompanied by the reduction of its serologic titer as specific blood group and by the liberation of dialyzable reducing substances, chiefly acetyl-glucosamine.

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SPANISH ABSTRACT

## Una Diferencia Bioquímica hasta hoy Desconocida entre la Leche Humana y la Leche de Vaca

El punto de partida de las investigaciones de los autores de este artículo ha sido uno de los problemas básicos en investigación pediátrica: leche huma versus leche de vaca. Esta es una comunicación preliminar de este aspecto.

Los niños alimentados con leche humana en cantidades suficientes se distinguen por sí mismos de aquellos que reciben leche de vaca por una resistencia mayor, en general, a las infecciones, incluyendo no solamente las intestinales sino también las respiratorias. La pregunta acerca de si este efecto benéfico se debe a la alimentación al pecho o a la leche humana en sí, aún no ha recibido un análisis crítico intensivo en la literatura reciente.

La flora intestinal de un lactante normal alimentado al seno está caracterizada por la predominancia del Lactobacillus bifidus en contraste con la flora mixta de los lactantes alimentados con fórmulas de leche de vaca. El pH fecal del niño alimentado al pecho es claramente ácido y se desvía hacia la neutralidad ó aún alcalinidad en el alimentado con leche de vaca.

Los intentos para relacionar estas diferencias con las composiciones químicas distintas de la leche humana con la de vaca han tenido éxito sólo parcialmente. El empleo de las fórmulas de leche diluída de vaca adicionada de carbohidratos hasta las modificaciones más elaboradas de la leche de vaca para semejarla a la leche humana se basaron en este principio. Sin embargo, todas ellas han sido de carácter algo restringido, de acuerdo con los conocimientos actuales de la composición química de la leche humana y de la leche de vaca. Las diferencias químicas conocidas entre ambas leches, aunque significantes en varios aspectos, y aun cuando sean de lo más pronunciadas, están dentro del mismo orden de magnitud.

Durante los últimos tres años el esfuerzo de los autores se dirigió hacia el estudio de los requerimientos metabólicos del Lactobacillus bífidus tal como se aisló de las evacuaciones de niños tanto alimentados al seno como a la botella, logrando con éxito delinear un medio semi-sintético en el cual el bacilo podía ser mantenido indefinidamente, cuando menos por varios años, sin pérdida de sus cualidades morfológicas, metabólicas y serológicas más importantes.

En el curso de estas investigaciones los autores encontraron aparentemente una variedad de Lactobacillus bífidus por mutación específica que denominaron L. Bífidus var. Penn. aislado de las evacuaciones de un lactante alimentado al seno, que no crecía en el medio original en que se aisló y que es satisfactorio para el mayor número de cepas de bacilos bífidus. Requería para su desarrollo la adición de un "factor de crecimiento" específico, presente en la leche humana, pues cuando esta última se añadía al medio de cultivo original se desarrollaba muy satisfactoriamente. La leche de vaca tenía sólamente 1/30 a 1/100 de la actividad de la leche humana para producir el desarrollo de esta variante del Lactobacillus bífidus. La actividad promedio relativa fué más alta en el calostro humano, e inmediatamente después el calostro de la rata, en seguida la leche humana, leche de rata y calostro de vaca (tomado en el primer día). Todas las demás leches ensayadas, en particular la leche de rumiantes, como las ovejas y las cabras, así como la de vaca, mostraron una actividad muy escasa. Las leches de puerca y de yegua son un poco más activas y la del cobayo inactiva.

Este factor de crecimiento microbiológico es diferente de todas las vitaminas y factores de crecimiento conocidos. Los preparados de hígado solo tuvieron muy ligera actividad y la levadura y la carne prácticamente ninguna. El meconio es súmamente activo. El semen humano, moco cervical uterino, jugo gástrico (aun en un caso de anemia perniciosa), saliva, líquido amniótico y las lágrimas fueron también muy activas. Este factor de crecimiento se presenta en la leche humana bajo

la forma de pequeñas y grandes moléculas. En el meconio se encuentra en forma no dializable. Las substancias purificadas A y B de los grupos sanguíneos son intensamente activas. De la leche humana se obtuvieron productos levógiros activos que contenían N-acetil glucosamina, fucosa y galactosa, pero no se encontraron aminoácidos. La N-acetil-glucosamina y la N-acetil galactosamina fueron ligeramente activas, por el contrario, se encontró una actividad muy grande en los glucosidos de la N-acetil-d-glucosamina.

El Lactobacillus bífidus variedad Pennsylvania contiene una enzima específica que inactiva el factor microbiológico de crecimiento requerido por la misma cepa. La inactivación enzimática del meconio o de las substancias purificadas de los grupos sanguíneos como factores de crecimiento, se acompaña de la reducción de su título serológico como grupo sanguíneo específico y por la liberación de substancias dializables reducibles, principalmente acetil-glucosamina.

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# GALACTOCELE IN A MALE INFANT

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CYSTS of the breast in males are extremely rare and among these galactocele is reported only twice in the literature. One of these cases was in a 75 year old man and the other in a 14 month old child. In neither case is evidence presented as to the nature of the contents of the cyst except for the statement that the material resembled milk. Since it is difficult to identify milk, and since clinical reliance is placed upon the characteristic appearance of the liquid rather than upon its chemical properties, the present authors have confirmed the original impression that the content of the cyst reported here in a 17 month old child actually was milk.

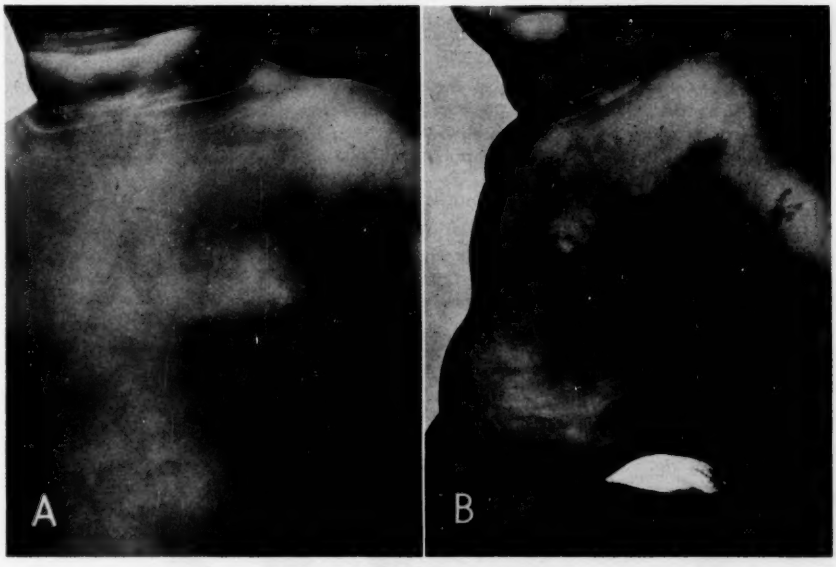


FIG. 1A and B—R. K. on admission.

## CASE REPORT

R. K., a 17 mo. old male infant, was brought to the clinic with the report that for 6 mo. there had been progressive enlargement of L. breast (see Fig. 1). Three months prior to admission red streaks were seen radiating from the nipple, but they disappeared shortly afterward. Patient had no symptoms from the enlargement and it appeared to be nontender. He was the only child of 31 yr. old mother and 45 yr. old father and had been a breech delivery. Birth weight was 3.9 kg. and

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his feeding, growth and development had been normal. At birth both breasts were only slightly enlarged and R. breast subsided in a short time. Left breast remained minimally enlarged. When he was about 1 yr. of age the breast began to increase in size rapidly.

On physical examination a soft, smooth, nontender mass was found in L. breast, about 5 cm. in diameter. It was fluctuant and transilluminated. No secretion or bleeding was seen. There was a small umbilical hernia, but no other findings of note. Both testes were in the scrotum and there was normal growth of hair and normal body structure or size.

At operation a thick-walled, fluctuant mass adherent to the skin but not to the pectoralis major was dissected out. It contained about 25 cc. of cloudy white fluid. There was no obvious inflammatory reaction. Except for a small hematoma in the incision, there was an uneventful postoperative course.

### Pathologic Report

Specimen consists of a spherical circumscribed cyst measuring 5.5 × 5.5 × 2 cm. The surface consists of adipose and fibrous tissue. On section about 10 cc. of homogeneous milky free-flowing fluid was released. Cyst is unilocular and wall is 2 mm. thick. Cyst lining is smooth and varies from red to pink.

Microscopic examination shows cyst to be lined by cuboidal epithelium, which in some areas is slightly flattened and elsewhere is tall with clear cytoplasm and ovoid nuclei. Wall of the large cyst is generally thin with some areas which measure up to 1 cm. In these areas numerous small cysts are present, the linings of which are similar histologically to that of main cyst. They are surrounded by loose edematous vascular stroma containing a few large arteries in which the walls are greatly thickened. There are only a few scattered single lymphocytes and no follicles are present or other features, which would be characteristic of a cystic hygroma. Sections are consistent with the diagnosis of galactocele. (Dr. T. Winship.)

### Chemical Analysis

Material received consisted of 2 tubes of white opaque fluid with a thick creamy semisolid upper layer. It resembled slightly soured milk, and had the characteristic odor of lactic acid. Protein content was 1.10%, fat content was 2.6% and sugar content was 2.4%. The sugar was non fermentable, gave a negative test for pentose, and a positive Rubner reaction.

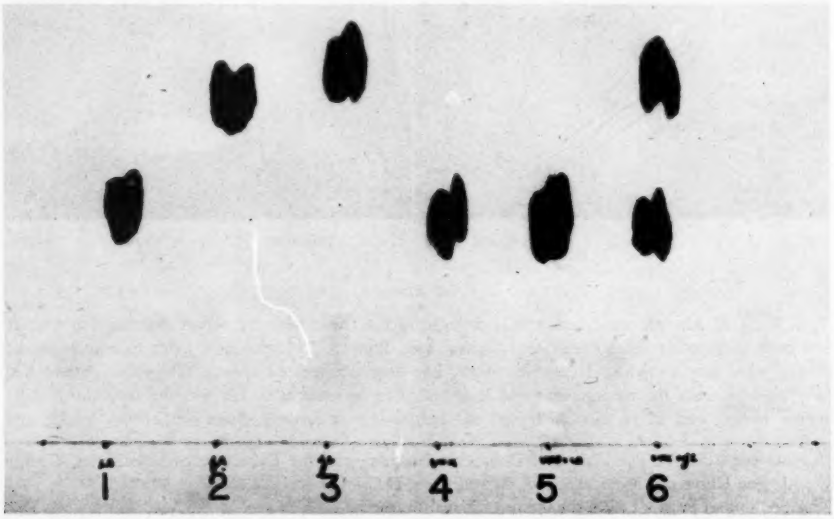


Fig. 2. Chromatogram comparing unknown sugar with known carbohydrates—10 gamma samples. 1. Lactose, 2. galactose, 3. glucose, 4. unknown, 5. unknown plus lactose, 6. unknown plus glucose.

Two milliliters of the opaque white fluid were deproteinized with picric acid and a reducing sugar crystallized from the filtrate by addition of 5 volumes of acetone. The 4.5 mg. of sugar so obtained were oxidized with nitric acid to yield 1 mg. of typical crystals of mucic acid, m.p. 223-225°C. (UNC) reported 223-224°.[1] Supernatant yielded a small amount of acid which formed a crystalline potassium salt, apparently potassium acid saccharate. As a final confirmation of this evidence that the sugar was lactose a protein-free filtrate of the fluid was prepared by precipitation with barium hydroxide and zinc sulfate, and subjected to paper chromatography,[2] using water-saturated phenol solvent. Spots were developed with aniline oxalate. Only a single spot could be demonstrated in the chromatogram of this filtrate, and it coincided with the standard lactose spot (Fig. 2).

## Discussion

Since lactose has never been found in any human secretion except that of a functioning mammary gland, the identification of this sugar in such material as was obtained from this cyst established its identity as milk or some derived mixture. Although the fluid has the qualitative characteristics of milk, the proportion of lactose, protein and fat is quite different from that of normal human milk (table 1).[3] Nordmann[4] described great variation in composition of galactoceles (table 1) and attempted to explain them with three

TABLE 1

Composition of Human Milk and of Galactocele Contents

| | Human Milk | Cysts | Authors' Case |
|---|---|---|---|
| Fat | 3.5 % | 2.5 to 38.8% | 2.6 % |
| Lactose | 7.5 % | 0 to 5.8% | 2.4 % |
| Protein | 1.25% | | 1.10% |

possible mechanisms. He suggested that cyst contents might be altered by infiltrating cells, by contaminating bacteria, or by selective absorption through the cyst wall. In the present case, the difference between the fluid found and human milk seems to be due to dilution of all the constituents. The rapid enlargement of this cyst and the "red streaks around the nipple" suggest that a small cyst containing about one fifth the volume of material found at operation was traumatized and, in the mild reaction to the injury, serous fluid entered the cavity and diluted its contents, at the same time expanding its volume.

The origin of the cyst remains obscure, with the best possibility being the theory of Nordmann, that inflammatory or neoplastic obstruction of ducts results in retention-type cysts. This leaves much to be desired, however, since there is usually resorption of the contents of engorged infant breasts, rather than emptying through the ducts.

Only two cases of galactocele have been reported in males. The first case, reported by Cattani,[5] was in an infant, 14 months of age. He describes a soft rounded fluctuant enlargement of the left breast of six months' duration. This lesion was nontender, and the patient was in excellent health. Drainage of the cyst yielded 30 cc. of milklike fluid, which showed globules of fat on microscopic examination. The child was brought back shortly afterward with a partial return of the swelling. A tight compress was applied for a few days and there was no further recurrence.

The other case reported was in a 75 year old male, who was seen by Velpeau.[6] One breast was greatly enlarged, and aspiration yielded a large quantity of fluid which appeared to be milk. This enlargement had been present for eight years.

The presence of a galactocele requires at least two factors not normally present in

males: competent secretory epithelium and pituitary hormonal stimulus. This would require both a high estrogen level and lactogenic hormone secretion. An increased level of estrogen might be expected in an elderly man, particularly if there were some liver impairment, but cannot be explained in the two infants. The presence of prolactin cannot be explained in any of the cases.

It seems, at present, that the most plausible hypothesis for the two similar cases in infants is that a small retention cyst containing about 5 to 10 cc. of milk formed in the neonatal period and remained quiescent for 8 to 10 months. Trauma then caused some inflammatory reaction, resulting in the loss of part of the lining of the cyst. Serous fluid then began to enter the cavity, and the original milk content was diluted about three-fold. In the case reported here the history of red streaks around the nipple and subsequent rapid growth lends itself to this interpretation. The analytic data suggest a dilution of the sugar of three-fold from normal milk. The relatively normal fat content and protein content could be due to degeneration of tissue and leakage of serous fluid. Thus we can explain the two cases in the infants without recourse to unusual hormonal secretions. The case of the galactocele in the elderly man, and indeed the question of whether the liquid found by Velpeau was really milk, is not clear.

## Summary

A case of a galactocele in a 17 month old male is reported with identification of the sugar contained in it as lactose.

A hypothesis for the formation of the infantile form of galactocele is presented.

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## Spanish Abstract

### Galactocele en un Niño

Los autores relatan el caso de un niño de 17 meses de edad cuyo pecho izquierdo comenzó a crecer rápidamente a la edad de un año. Ambos pechos estaban solo ligeramente aumentados de volumen cuando el niño nació; el del lado derecho decreció en poco tiempo pero el del izquierdo permaneció crecido aunque mínimamente. Se encontró a la exploración una tumoración blanda, regular, no dolorosa, situada en el pecho izquierdo, de unos 5 cm. de díametro, fluctuante y que se transluminaba. Al extirparlo se demostró una masa fluctuante de paredes gruesas adherente a la piel, que contenía unos 25 c.c. de líquido blanco turbio.

El estudio histológico demostró tratarse de un galactocele y el análisis del líquido permitió probar que contenía lactosa.

La revisión de la literatura solo revela otros dos casos de galactocele en individuos de sexo masculino, uno en un niño de 14 meses y otro en un anciano de 75 años.

Se sugiere la hipótesis de que los quistes formados en el periodo neonatal estuvieron presentes por varios meses sin crecer y que un trauma produjo una reacción inflamatoria que causó pérdida parcial de su pared de revestimiento permitiendo así la entrada de líquido seroso dentro de la cavidad y diluyendo su contenido original de leche produciendo su crecimiento rápido.

# HERPANGINA: CLINICAL AND LABORATORY ASPECTS OF AN OUTBREAK CAUSED BY GROUP A COXSACKIE VIRUSES

*By* LILLIAN P. KRAVIS, M.D., KLAUS HUMMELER, M.D., M. MICHAEL SIGEL, PH.D., and HAROLD I. LECKS, M.D.
*Philadelphia*

DURING the summer of 1950, Huebner and his associates[1] recovered several group A Coxsackie viruses from patients in Parkwood, Md., and Washington, D.C., ill with a disease which resembled clinically an entity described in 1920.[2,3] This disease entity of unknown etiology had been given the name herpangina. Huebner adopted this name and produced evidence which causally linked the Coxsackie group A viruses to herpangina. This was the first convincing indication that the Coxsackie viruses might cause a specific human disease. The purpose of this publication is to describe a similar outbreak of herpangina in Philadelphia which occurred in 1951 and from which Coxsackie group A viruses of three immunologic types were isolated.

## DESCRIPTION OF THE CLINICAL AND EPIDEMIOLOGIC ASPECTS OF THE OUTBREAKS

The first patient in the series, J. T., a 7 yr. old girl, on the evening previous to first examination had suddenly developed fever of 40.0° C. Patient had no other complaints until the following day when she complained of a sore throat. At this time, multiple petechial lesions were visible on tonsillar pillars and soft palate. When seen again on next day, these lesions had ulcerated. Ulcers were gray-based and outlined by red areolas. She was afebrile and asymptomatic by fourth day. It was learned that she had been in close contact with another child shortly before the latter had developed a similar illness 4 days previously.

In rapid succession, J. T.'s sister, A. T., and a close friend, R. C., developed similar lesions in oropharynx although their illness differed from J. T.'s in that A. T. had a small ulcer on tip of her tongue in addition to faucial ulcers, and R. C. ran a completely afebrile course. No further cases were seen by the authors in this community although discussions with other practicing physicians led to the belief that many cases of an illness almost identical with the above did occur in this area.

S. M., a 4½ yr. old child living in an opposite part of town, attended a nursery school with an enrollment of 70 children between ages of 3 and 9 yr. S. M. became ill in school early in the morning. On her return home at noontime, she had fever of 38.8° C. and complained of a sore throat. When she was examined in late afternoon temperature was normal. One small ulcer was present on R anterior tonsillar pillar. By following day, several more ulcers were present.

Illnesses of almost identical description appeared in 2 contacts of S. M. in the nursery school on 4 days and 10 days later, respectively (S. F. and B. C.). Another child in both households of S. M. and of one of her contacts, B. C., also became ill with fever and sore throat subsequently (M. C. and B. M.). Two other children in the nursery school were absent from sessions because of fever and sore throat after S. M.'s illness, but the actual extent of absences from the school attributable to illness was difficult to assess since no attendance records were kept during summer months.

From each of the cases mentioned above, the same type of Coxsackie group A virus was isolated from throat swabs or feces, or both.

In addition, 9 children residing in different parts of town were seen with clinical pictures re-

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TABLE 1

TYPE AND SOURCE OF COXSACKIE GROUP A VIRUSES

| Case | Age | Sex | Date of Onset | Type Virus | Source of Virus: Stool Days After Onset | Stool Result | Throat Days After Onset | Throat Result | Comment |
|---|---|---|---|---|---|---|---|---|---|
| J. T. | 7 yr. | F | 6/29/51 | H 3 | 5 | + | 4 | + | |
| R. C. | 8 yr. | F | 6/30/51 | H 3 | 3 | + | 2 | − | Played with J. T. Course afebrile |
| A. T. | 2 yr. | F | 7/ 2/51 | H 3 | 2 | + | 1 | + | Sister J. T. |
| J. L. | 11 yr. | M | 7/ 8/51 | H 3 | 3 | + | 3 | + | |
| S. M. | 4½ yr. | F | 7/18/51 | H 3 | 11 | + | 1 | + | |
| B. M. | 11 mo. | M | 7/27/51 | H 3 | 2 | + | ND | ND | Brother S. M. |
| S. F. | 6½ yr. | F | 7/22/51 | H 3 | 9 | + | ND | ND | Attended same school as S. M. |
| B. C. | 3 yr. | M | 7/27/51 | H 3 | 7 | + | ND | ND | Attended same school as S. F. and S. M. |
| M. C. | 17 mo. | M | 7/31/51 | H 3 | 3 | + | ND | ND | Brother B. C. |
| A. deF. | 2 yr. | M | 7/16/51 | H 3 | 10 | − | 3 | + | |
| R. K. | 3½ yr. | M | 7/22/51 | H 3 | 2 | + | 2 | + | |
| R. M. | 8 yr. | F | 7/20/51 | H 3 | ND | ND | 3 | + | |
| M. K. | 2½ yr. | F | 7/22/51 | H 3 | 3 | + | ND | ND | Sister R. K. |
| R. S. | 2½ yr. | F | 7/26/51 | Dalldorf Type 2 | 4 | + | 4 | + | |
| R. M. | 7 mo. | M | 7/24/51 | High Point | 31 | − | 4 | + | |
| J. B. | 4½ yr. | F | 8/ 6/51 | High Point | 2 | + | ND | ND | |
| W. D. | 3½ yr. | M | 8/27/51 | High Point | 2 | + | 2 | + | |

TABLE 2

SEROLOGIC STUDIES OF HOMOLOGOUS COXSACKIE ANTIBODY LEVELS IN PATIENTS FROM WHOM VIRUS WAS RECOVERED

| Case | Acute Phase Serum: Days After Onset | Antibody Titer CF* | Antibody Titer NT† | Convalescent Phase Serum: Days After Onset | Antibody Titer CF | Antibody Titer NT |
|---|---|---|---|---|---|---|
| R. C. | 2 | <4 | <50 | 26 | 8 | 180 |
| W. D. | 2 | <6 | <25 | 88 | 48 | >200 |
| R. S. | 2 | <4 | <25 | 139 | 8 | 300 |
| R. M. 8 yr. | — | — | — | 41 | <2 | 100 |
| R. M. 7 mo. | — | — | — | 31 | 24 | >200 |

* Expressed as reciprocal of highest serum dilution to give 3+ or 4+ fixation of complement in presence of fixed amount of antigen.

† Expressed as reciprocal of highest serum dilution to give complete neutralization of 100 ID50 units of homologous virus.

sembling the above-described. From all of these Coxsackie group A virus strains were isolated which fell into 1 of 3 immunologic types. The pertinent features of these cases are summarized in table 1. The 17 children comprising the tabulated group ranged in age from 7 mo. to 11 yr. Nine were females and 8 males.

In 4 instances, there were multiple infections within the same household. In 2 of these households, an infant developed signs of disease within 3 and 4 days, respectively, after the onset of infection in an older child. In one household, 2 siblings became ill simultaneously and in still another household, an infant contact of an older sibling developed conjunctivitis 9 days after onset of his sister's infection, and at this time virus was isolated from his stool. Since no attempt was made to recover virus from this child's eyes, it cannot be assumed that the isolated virus caused this conjunctivitis, although Huebner et al. have noted conjunctivitis as a feature of some cases of herpangina.

TABLE 3

DETERMINATION OF COMPLEMENT-FIXING AND NEUTRALIZING ANTIBODIES TO SEVERAL PROTOTYPE COXSACKIE VIRUSES IN SERA OF PATIENTS WITH HERPANGINA

| Patient | Type of Virus Isolated | No. of Days After Onset | Viruses | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | $H_3$ | | Dalldorf 2 | | High Point | |
| | | | CF* | NT† | CF | NT | CF | NT |
| W. D. | High Point | 2 | <6 | — | <6 | — | <6 | <25 |
| | | 88 | <6 | — | <6 | — | 48 | >200 |
| | | 9 mo. | — | — | — | — | <2 | — |
| R. S. | Dalldorf 2 | 2 | <4 | — | <4 | <25 | <4 | <25 |
| | | 139 | <4 | — | 8 | 300 | <4 | <50 |
| R. C. | $H_3$ | 2 | <2 | <50 | <6 | <50 | <6 | 50 |
| | | 26 | 16 | 180 | <6 | 200 | 16 | >200 |
| R. M. 7 mo. | High Point | 31 | <6 | <25 | <6 | — | 24 | >200 |

* Expressed as reciprocal of highest serum dilution to give 3+ or 4+ fixation of complement in presence of fixed amount of antigen.

† Expressed as reciprocal of highest serum dilution to give complete neutralization of 100 ID50 units of homologous virus.

— Not tested.

Three mothers of infected children carried virus of the same type as their children's in their stools. In the case of 2 mothers on whom serum specimens were obtained, neutralizing antibody titers in specimens drawn during the child's convalescence were of low magnitude in comparison with those of the infected children, and complement fixation tests yielded equivocal results. All these adults were symptom-free at the time when the virus was recovered, thus illustrating the fact that inapparent infections or silent carrier-states do occur in the course of an epidemic.

One of the 3 mothers was a laboratory associate. Twenty days after she entered upon this investigation of herpangina, her 2 children, aged 2½ yr. and 3½ yr., awakened with complaints of fever and muscle soreness. During the course of that day, both children developed lesions characteristic of herpangina, and type H3 Coxsackie virus was recovered from stools of both, and from a throat swab of one. The same type virus was recovered from a specimen of the mother's stool obtained 3 days after the children's positive specimens were obtained. Unfortunately, no previous stool specimens from mother or children had been examined nor were serologic studies possible. However, since there was no history of any herpangina-like illness among the playmates of the 2 children prior to the onset of their illnesses, the mother is believed to be the source of the children's infections.

## Laboratory Studies

1. Isolation of Virus

A. Materials and Methods: Three types of specimens were used: throat swabs, rectal swabs and feces. Throat or rectal swabs were made with sterile cotton-tipped applicators and placed in sterile buffered saline or beef broth and frozen immediately at —20° C. Feces were frozen immediately at —20° C. when possible or refrigerated overnight and frozen next morning when facilities for immediate freezing were not available.

Just prior to inoculation the specimens were thawed, suspended in sterile saline or broth, and treated with penicillin and streptomycin. Quantities of 0.04 cc. were inoculated intraperitoneally into 1 litter of 1 to 4 day old mice. Whenever paralysis occurred, paralyzed mice in each litter were removed, etherized and frozen at —20° C. immediately.

From paralyzed mice of each primary isolation, a 20% suspension of carcass was prepared in a Waring blendor after removal of skin, head, limbs and viscera. This first passage mouse suspension was centrifuged at 2000 rpm for 30 min. and supernatant material frozen at —20° C.

In each instance, presence of virus was substantiated on 2nd mouse passage through 1 to 4 day old mice. Whenever paralysis occurred it was flaccid in type, involving primarily the hind limbs of mice.

B. Results: From 17 patients included in this series, 24 virus isolations were accomplished. In table 1, individual isolations from various sources are related to time after onset of illness that specimens were collected. Although in majority of patients, throat swabs, feces or rectal swabs were taken within 1st 3 days of illness, virus was recovered from 3 throat swabs as late as 4th day after onset of symptoms. Virus is known to persist for some time in stools of patients infected with Coxsackie virus and in the authors' experience, was recovered from feces as late as 11th day after onset of illness.

2. Identification of Virus

As mentioned above, presence of virus in stools and throat swabs was established by virtue of the flaccid paralysis which developed in suckling mice following inoculation of these materials. This paralysis in itself was highly suggestive of the fact that isolated agents belonged to the Coxsackie group.

In order to meet the other criteria of identification, the following tests were done:

A. Histopathologic Sections of Paralyzed Muscles: Thigh muscles of several paralyzed mice were examined. Sections showed muscle degeneration described by others in Coxsackie virus infection of baby mice.[3, 4, 5]

B. Inoculation of Isolated Strains into Adult Mice: Several strains were inoculated into 30 day old mice by both intracerebral and intraperitoneal routes. Size of inoculum was 0.04 cc. intracerebrally and 0.2 cc. intraperitoneally. In no instance did these animals show signs of illness subsequently.

C. Exclusion of Infection with Herpes Simplex Virus: Furthermore, infection with one other virus which may produce throat lesions similar to those encountered in these children, namely, herpes simplex virus, was excluded. Throat swabs from 8 of 17 patients were submitted to the Skin Virus Laboratory in this hospital for attempts at herpes simplex virus isolation.* Many of these specimens were passaged 3 or more times on chorioallantoic membranes of embryonated hens' eggs but all were negative for presence of virus.

3. Typing of Virus

In all instances original typing of strains was performed at the National Institutes of Health in Bethesda, Md. When materials later became available for immunologic classification of strains in the Virus Diagnostic Laboratory of The Children's Hospital of Philadelphia, results of original typing were confirmed in every case. Typing was accomplished both in the Bethesda and Philadelphia laboratories by testing mouse-carcass suspensions containing virus of an unknown type against specific mouse or hamster immune sera in complement-fixation and mouse-neutralization tests.

A. Materials and Methods: Technics of preparation of antigens, antisera and of complement-fixation and neutralization tests will be described elsewhere.[6]

B. Results of Typing: The 24 isolated viruses were found to fall into 1 of 3 Coxsackie group A prototypes; namely, $H_3$, Highpoint and Dalldorf, type II, as indicated in tables 1 and 3. Majority of strains were of $H_3$ type.

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* The authors wish to acknowledge their indebtedness to Dr. T. F. McNair Scott for the herpes virus isolation attempts.

4. Serologic Studies on Human Sera

An effort was made to prove that viruses isolated from these patients with clinical herpangina were causative agents of the disease by demonstrating a rise in homologous antibody titers in paired serum specimens. Unfortunately, it was impossible to obtain such paired specimens from more than 3 patients. In 2 additional patients, single specimens were drawn during convalescence. In the above 5 patients, both complement-fixation and mouse-neutralization tests were performed with homologous virus antigens. Results of these tests are recorded in table 2. Serum specimens from 4 of the 5 patients were tested against more than one antigen. Results of such multiple-antigen neutralization and complement-fixation tests are shown in table 3. Three of the 4 patients tested developed a significant specific antibody response for the homologous virus antigen.

The fourth patient, R. C., also showed a rising antibody titer against virus isolated from stool specimen, but in addition, antibody-titer rises of equal magnitude were noted when her serum was tested against 2 immunologically different Coxsackie group A antigens. This type of multiple serologic response may be explained in at least 2 ways: (1) Patient may have been infected with 3 different types of Coxsackie virus simultaneously or consecutively. Although simultaneous or concurrent infection with 3 types has not been reported, concurrent infection with 2 types was described by Beeman et al.[4] (2) Patient may have been exhibiting a group-specific serologic type of response to infection with the single strain of Coxsackie virus that was recovered. The appearance of antibodies to several types of Coxsackie viruses in what appear to have been infections with only one type Coxsackie virus has been recorded by others,[4,7] but it has not been determined whether this type of reaction may occur in response to infection with agents other than Coxsackie viruses as well.

Unfortunately, the only attempt at virus isolation from a throat swab made during the acute phase of this patient's illness was unsuccessful. It is not known whether additional attempts to isolate virus from throat lesions might have yielded Coxsackie viruses, immunologically different from the one isolated from stool.

## Discussion

The investigation of several small outbreaks of a disease resembling the clinical entity, herpangina, confirm the work of Huebner et al. which established the etiologic relationship of certain Coxsackie group A viruses to this disease. Three immunologic types of group A Coxsackie virus were isolated from 17 of 21 children. Rises in homologous serum antibody titers were demonstrated in three of these children during convalescence. The causal relationship of the recovered viruses to herpangina was further suggested by failure to isolate Coxsackie virus from throat swabs taken from 22 patients with nonspecific mouth lesions, fevers of unknown etiology or neurologic illnesses suggestive of nonparalytic poliomyelitis. The circumstances under which two children of one of the authors of this communication simultaneously developed herpangina suggest that an inapparently infected laboratory worker or other adult can transmit the virus to children. The same immunologic type of Coxsackie virus, i.e., $H_3$, which was isolated from the first patients in this group, was also recovered from the asymptomatic investigator and her 2 children with herpangina.

Although there are as yet few reports of herpangina in the literature,[1,8,9] the disease must be widespread since serologic surveys conducted on a large scale by several investigators[10,11] indicated that antibodies against viral strains recovered from patients with herpangina are quite prevalent. Probably its mildness, freedom from complications and short duration, account for the minimal attention given to herpangina. These features may also explain why isolation of group A Coxsackie virus strains during the course of various illnesses occurring predominantly in the summer months have led to the association of these viruses etiologically with a variety of diseases. It is conceivable that herpangina could precede or occur concomitantly with another unrelated disease, yet be overlooked as an entity because of its mildness or its ill-defined clinical picture.

Isolation of virus from the stool and the development of antibodies in the blood could be misconstrued easily under such circumstances, as evidence that a given illness was caused by Coxsackie virus. Actually recovery of virus and concurrent development of antibody merely indicate infection with Coxsackie virus. Before taking the next step and labelling the isolated virus as the cause of the disease in question, a number of clinical and epidemiologic requirements must be met, as they were in the classical investigation of Huebner et al.[1] on herpangina.

The question of which diseases the different Coxsackie viruses cause remains unsettled. To date only herpangina and epidemic pleurodynia definitely seem to be related causally to the Coxsackie viruses. For this reason this laboratory limits the performance of routine Coxsackie tests to instances in which either of these diseases is suspected. When herpangina is the disease in question, laboratory confirmation of the diagnosis requires isolation of virus from the throat lesions. Demonstration of a rising antibody titer to the isolated virus adds further confirmatory evidence.

When the virus is recovered from the stool alone or when no virus is recovered, or when only a serologic response to a Coxsackie virus strain is demonstrated, the laboratory data would be considered insufficient for diagnosis.

More thorough clinical and laboratory studies on herpangina should help to clarify the role of the group A Coxsackie viruses in the production of this and other diseases in humans.

## Summary

The causal relationship between certain Coxsackie group A viruses and the disease entity herpangina first reported by Huebner and his associates in 1951 is confirmed.

Outbreaks of herpangina in Philadelphia during the summer of 1951 are described.

Coxsackie group A viruses of three different immunologic types were isolated from stools or throat swabs, or both, obtained from 17 of the 21 patients involved in the outbreaks.

A rise in complement-fixing and neutralizing antibody titers against homologous virus strains during convalescence was demonstrated in 3 patients.

Asymptomatic carriers of Coxsackie group A virus are described. Evidence is presented suggesting that two children with herpangina acquired their infection from such a carrier.

The criteria used in making a laboratory diagnosis of infection with Coxsackie virus are discussed.

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SPANISH ABSTRACT

## Herpangina: Aspectos Clínicos y de Laboratorio de un Brote Causado por Virus Coxsackie del Grupo A

En 1950 Huebner aisló varios virus coxsackie del Grupo A, de algunos enfermos cuyo padecimiento semejaba clínicamente una entidad descrita bajo el nombre de herpangina 30 años atrás. Se tuvo así la primera indicación convincente de que los virus coxsackie podrían causar una enfermedad humana específica. Los autores de este artículo describen un brote similar de herpangina que ocurrió en 1951 en la ciudad de Philadelphia y de cuyos enfermos aislaron 3 tipos inmunológicos de virus coxsackie del Grupo A, confirmando la relación causal entre estos virus y la entidad patológica herpangina, que Huebner postuló en 1950. En total hubo 21 casos en los brotes estudiados y el primero de ellos fué el de una niña de 7 años que 24 horas antes de ser examinada tuvo subitámente fiebre de 104° F, sin ninguna otra queja. Al siguiente día por la tarde se quejó de dolor de garganta y presentaba lesiones petequiales múltiples en los pilares amigdalinos y velo del paladar. A las 48 horas, dichas lesiones estaban ulceradas, su fondo era gris, estaban limitadas por una aureola roja. Al tercer día de enfermedad la niña estaba asintomática y afebril. Los padres informaron que el enfermo había estado en contacto íntimo con otro niño que pocos días antes tuvo un padecimiento semejante. Casos similares aparecieron en otras partes de la ciudad.

En 17 de estos 21 casos se aislaron virus coxsackie del Grupo A de las evacuaciones del exudado faringeo o ambos, que cayeron dentro de tres tipos inmunológicos diferentes.

En tres de los enfermos se demostró durante su convalescencia una elevación en los títulos de anticuerpos neutralizantes y de fijación del complemento en contra de cepas homólogas de virus y en 2 casos más les fué posible demostrar títulos altos de anticuerpos neutralizantes durante la convalescencia.

La presencia de portadores silenciosos de los virus encontrados se demostró en 3 madres de los niños infectados en los cuales pudo aislarse de sus evacuaciones el mismo tipo de virus cuando estaban asintomáticas. Una de dichas madres se cree que haya sido la fuente de la infección de sus dos niños dado que no pudo encontrarse otra fuente de contagio y la madre tenía en sus evacuaciones el mismo tipo de virus de sus hijos a los 3 días de que en ellos fué posible aislarlos.

Para establecer definitivamente el diagnóstico de herpangina se requiere la confirmación de laboratorio con el aislamiento del virus de las lesiones de la garganta y la demonstración de títulos de anticuerpos en aumento en contra del virus aislado es una prueba confirmatoria adicional. Si el virus se encuentra solamente en las evacuaciones, o no se aisla o solo se demuestra la respuesta serológica a una cepa de virus coxsackie, estos datos de laboratorio deben considerarse insuficientes para hacer el diagnóstico.

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# FUNCTION OF ADRENAL CORTEX IN PREMATURE INFANTS

## 1. Infants Without Recognized Disease

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THE peculiarities of adrenal gland development in man and other primates are of unknown physiologic significance. The gland is prominent throughout fetal life and is composed largely of a zone of tissue which abruptly involutes and disappears after birth. This is the fetal zone of the adrenal gland; a review of the information pertaining to its life cycle and possible physiologic roles has been compiled by the writer.[1] Several investigators have suggested that the fetal zone performs one of the functions of the adult-type cortex, though proof is lacking. The present study attempts to determine whether it produces corticosteroids; if the fetal zone is an important source of these hormones, a drop in the urinary excretion of formaldehydogenic steroids might be found during the time of its degeneration. Involution commences usually within 24 to 48 hours after birth and is maximal during the second and third weeks of post-natal life. The study therefore centers on the first 3 weeks of life.

### METHODS

Urinary formaldehydogenic steroid excretion was measured by method of Corcoran and Page.[2] Results are expressed as mg. of desoxycorticosterone equivalent (mg.DOC $\simeq$) both as total 24 hr. excretion and as excretion/24 hr./$m^2$ body surface calculated by Meeh's formula[3] ($S.A. = k^2\sqrt{wt^3}$) with Benedict and Talbot's[4] values for k (k is 10.0 in weight range of infants studied). Sodium and K in formula, stool and urine were determined with a flame photometer. Nitrogen was determined by Kjeldahl[5] method. Eosinophile counts were done from capillary blood with U. S. Bureau of Standards-certified pipettes and counting chambers, counting 4 chambers of 0.1 mm. depth and using phloxine-propylene glycol diluent.[6] Specially trained nurses prepared formulae during balance periods and made separate urine and stool collections on both male and female infants. Birth day extended from time of birth to the next 8:30 A.M.; first day of life was next 24 hr. period beginning at 8:30 A.M.

### RESULTS

#### 1. Urinary Formaldehydogenic Steroid Excretion

One hundred twenty-five determinations of formaldehydogenic steroids were made on urine from 8 premature infants without recognized disease during their 1st 64 days of life. Results are presented in figure 1 and chart 1. The trend of values was determined from regression lines calculated for each infant, both for 1st 10 days of life and for the whole period of observation. No significant trend was found in 1st 10 days, but over the entire period of observation in each case there was an increasing excretion with age. Average correlation coefficient was $r = -0.61$ with 95% confidence limits of $-0.72$ and $-0.47$. Probability of observed increase occurring by chance if there were no relationship to age is less than 1:1000.

Values obtained for infants were compared with those of adults. Mean level of formaldehydogenic

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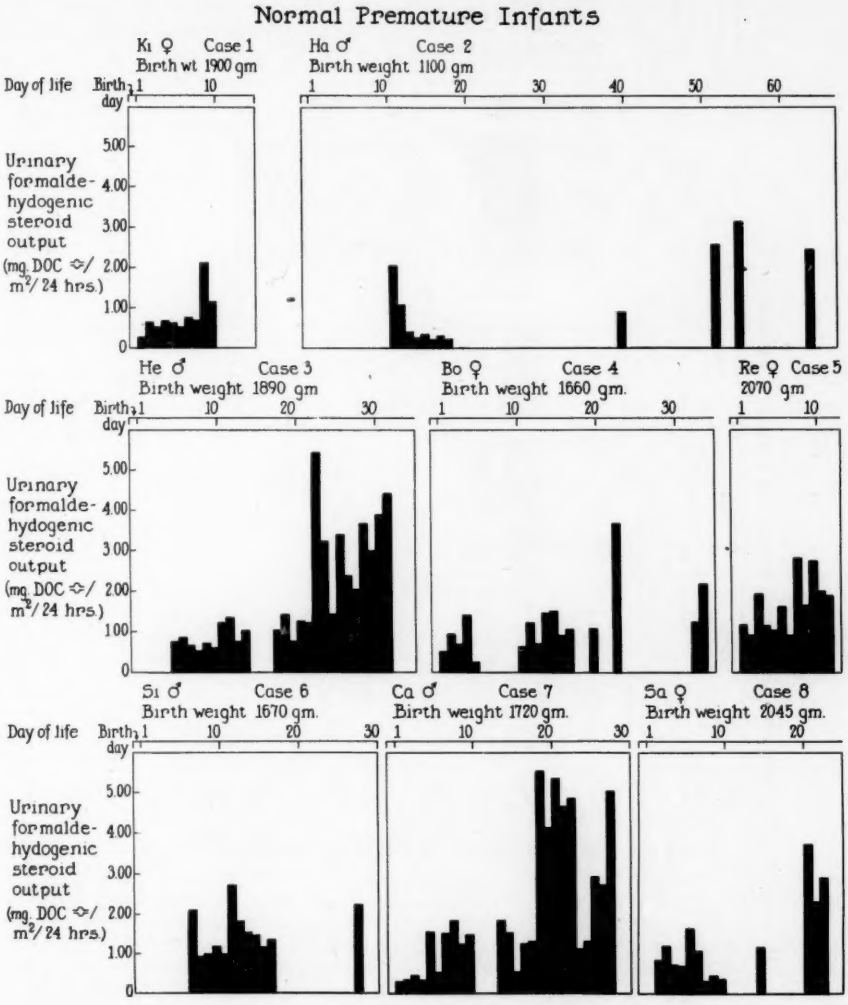
Normal Premature Infants
Ki ♀ Case 1
Birth wt 1900 gm
Ha ♂ Case 2
Birth weight 1100 gm
Day of life
Birth day
Urinary formaldehydogenic steroid output (mg. DOC ⇔/ m²/24 hrs.)
He ♂ Case 3
Birth weight 1890 gm
Bo ♀ Case 4
Birth weight 1660 gm.
Re ♀ Case 5
2070 gm
Si ♂ Case 6
Birth weight 1670 gm.
Ca ♂ Case 7
Birth weight 1720 gm.
Sa ♀ Case 8
Birth weight 2045 gm.

FIG. 1. Urinary formaldehydogenic steroid excretion.
Urinary excretion of formaldehydogenic steroids by 8 normal premature infants.

steroid excretion in 9 normal male young adults was determined by same method and found to be 0.87 mg. DOC⇔/m²/24 hr. with a standard error of 0.10 mg. Mean steroid excretion/m² body surface in early postnatal period was calculated from values for 5 infants, 4 on 1st day of life and 1 on 2nd; mean was 0.67 mg. with a standard error of 0.17 mg. Mean steroid excretion on 10th day of life, calculated from values in 7 infants, was 1.17 mg. with a standard error of 0.30 mg. These values are not significantly different from the mean in adults. Comparison after 10th day was not possible because of regression, with too few values for a valid comparison.

2. Nitrogen, Sodium and Potassium Balance Study

Data from a balance study for Na, K, and N in one infant are summarized in figure 2. Top 3

## CHART 1

### Urinary Excretion of Formaldehydogenic Steroids by Premature Infants

| Day of Life | Case 1 | | | Case 2 | | | Case 3 | | | Case 4 | | | Case 5 | | | Case 6 | | | Case 7 | | | Case 8 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | | Wt. (gm.) | mg.DOC ⇔/24 hr. | |
| | | Total | /m² | | Total | /m² | | Total | /m² | | Total | /m² | | Total | /m² | | Total | /m² | | Total | /m² | | Total | /m² |
| Birth Day | 1900 | | | 1100 | | | 1890 | | | 1660 | | | 2070 | | | 1670 | | | 1720 | | | 2045 | | |
| 1 | 1850 | 0.05 | 0.35 | | | | | | | | 0.08 | 0.54 | | 0.20 | 1.20 | | | | | 0.05 | 0.31 | | | |
| 2 | 1800 | 0.09 | 0.62 | | | | 1850 | | | 1660 | 0.14 | 0.99 | 1980 | 0.16 | 0.99 | | | | 1640 | 0.05 | 0.37 | 1920 | 0.14 | 0.93 |
| 3 | 1810 | 0.08 | 0.57 | | | | 1810 | | | 1540 | 0.10 | 0.72 | 1950 | 0.31 | 1.96 | | | | 1670 | 0.06 | 0.45 | 1870 | 0.18 | 1.20 |
| 4 | 1820 | 0.10 | 0.69 | | | | 1770 | | | 1520 | 0.19 | 1.42 | 1955 | 0.18 | 1.16 | | | | 1700 | 0.05 | 0.37 | 1910 | 0.11 | 0.74 |
| 5 | 1810 | 0.10 | 0.65 | | | | 1740 | 0.11 | 0.79 | 1500 | 0.04 | 0.27 | 1990 | 0.17 | 1.07 | | | | 1730 | 0.23 | 1.58 | 1910 | 0.11 | 0.72 |
| 6 | 1810 | 0.08 | 0.55 | | | | 1800 | 0.13 | 0.89 | | | | 1990 | 0.26 | 1.66 | | | | 1740 | 0.08 | 0.58 | 1990 | 0.26 | 1.66 |
| 7 | 1810 | 0.11 | 0.77 | | | | 1850 | 0.10 | 0.68 | | | | 1960 | 0.15 | 0.96 | 1560 | 0.28 | 2.11 | 1800 | 0.23 | 1.54 | 2010 | 0.17 | 1.09 |
| 8 | 1880 | 0.11 | 0.70 | | | | 1840 | 0.08 | 0.55 | | | | 1990 | 0.45 | 2.83 | 1570 | 0.13 | 0.93 | 1800 | 0.27 | 1.82 | 2020 | 0.05 | 0.34 |
| 9 | 1890 | 0.33 | 2.13 | | | | 1820 | 0.11 | 0.73 | | | | 2005 | 0.26 | 1.67 | 1640 | 0.14 | 0.99 | 1860 | 0.19 | 1.23 | 2090 | 0.07 | 0.42 |
| 10 | 1910 | 0.18 | 1.16 | | | | 1850 | 0.10 | 0.64 | 1580 | 0.09 | 0.64 | 2025 | 0.44 | 2.78 | 1670 | 0.17 | 1.19 | 1920 | 0.22 | 1.44 | 2100 | 0.06 | 0.37 |
| 11 | | | | 830 | 0.18 | 2.02 | 1880 | 0.19 | 1.26 | 1580 | 0.17 | 1.23 | 2095 | 0.33 | 2.01 | 1650 | 0.14 | 0.99 | 1970 | | | | | |
| 12 | | | | 850 | 0.10 | 1.08 | 1870 | 0.21 | 1.38 | 1550 | 0.10 | 0.72 | 2025 | 0.31 | 1.94 | 1710 | 0.39 | 2.74 | 2000 | | | | | |
| 13 | | | | 870 | 0.04 | 0.40 | 1900 | 0.12 | 0.78 | 1590 | 0.20 | 1.50 | | | | 1740 | 0.26 | 1.82 | 2030 | | | | | |
| 14 | | | | 900 | 0.03 | 0.29 | 1920 | 0.16 | 1.05 | 1620 | 0.21 | 1.52 | | | | 1730 | 0.23 | 1.58 | 2070 | 0.29 | 1.81 | | | |
| 15 | | | | 880 | 0.03 | 0.36 | 1950 | | | 1650 | 0.13 | 0.94 | | | | 1790 | 0.22 | 1.50 | 2150 | 0.26 | 1.54 | 2290 | 0.20 | 1.18 |
| 16 | | | | 910 | 0.02 | 0.21 | 1990 | | | 1690 | 0.15 | 1.06 | | | | 1780 | 0.17 | 1.18 | 2200 | 0.10 | 0.57 | | | |
| 17 | | | | 1000 | 0.03 | 0.30 | 2030 | | | | | | | | | 1780 | 0.20 | 1.39 | 2300 | 0.22 | 1.24 | | | |
| 18 | | | | 1000 | 0.02 | 0.22 | 2070 | 0.17 | 1.04 | | | | | | | | | | 2340 | 0.23 | 1.30 | | | |
| 19 | | | | | | | 2120 | 0.23 | 1.42 | 1830 | 0.16 | 1.08 | | | | | | | 2370 | 0.99 | 5.55 | | | |
| 20 | | | | | | | 2140 | 0.13 | 0.80 | | | | | | | | | | 2420 | 0.75 | 4.17 | | | |
| 21 | | | | | | | 2190 | 0.22 | 1.29 | | | | | | | | | | 2500 | 0.99 | 5.38 | 2500 | 0.69 | 3.75 |
| 22 | | | | | | | 2190 | 0.21 | 1.24 | 1960 | 0.59 | 3.73 | | | | | | | 2520 | 0.87 | 4.68 | 2440 | 0.42 | 2.32 |
| 23 | | | | | | | 2230 | 0.93 | 5.44 | | | | | | | | | | 2590 | 0.92 | 4.88 | 2510 | 0.54 | 2.93 |
| 24 | | | | | | | 2260 | 0.56 | 3.23 | | | | | | | | | | 2640 | 0.22 | 1.13 | | | |
| 25 | | | | | | | 2290 | 0.25 | 1.42 | | | | | | | | | | 2660 | 0.26 | 1.34 | | | |
| 26 | | | | | | | 2340 | 0.60 | 3.40 | | | | | | | | | | 2770 | 0.59 | 2.97 | | | |
| 27 | | | | | | | 2370 | 0.43 | 2.39 | | | | | | | | | | 2840 | 0.56 | 2.76 | | | |
| 28 | | | | | | | 2390 | 0.37 | 2.04 | | | | | | | 2290 | 0.39 | 2.22 | 2870 | 1.02 | 5.05 | | | |
| 29 | | | | | | | 2530 | 0.68 | 3.68 | | | | | | | | | | | | | | | |
| 30 | | | | | | | 2520 | 0.56 | 3.00 | | | | | | | | | | | | | | | |
| 31 | | | | | | | 2570 | 0.74 | 3.91 | | | | | | | | | | | | | | | |
| 32 | | | | | | | 2630 | 0.84 | 4.42 | | | | | | | | | | | | | | | |
| 33 | | | | | | | | | | 2230 | 0.22 | 1.27 | | | | | | | | | | | | |
| 34 | | | | | | | | | | 2240 | 0.38 | 2.19 | | | | | | | | | | | | |
| 40 | | | | 1640 | 0.13 | 0.91 | | | | | | | | | | | | | | | | | | |
| 52 | | | | 2200 | 0.44 | 2.57 | | | | | | | | | | | | | | | | | | |
| 55 | | | | 2200 | 0.53 | 3.13 | | | | | | | | | | | | | | | | | | |
| 64 | | | | 2530 | 0.45 | 2.42 | | | | | | | | | | | | | | | | | | |

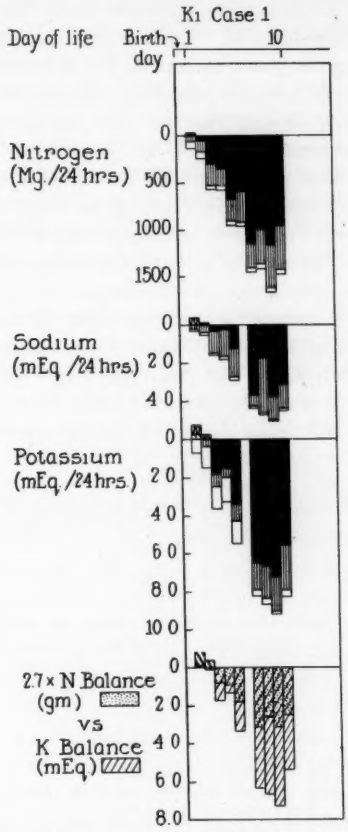


FIG. 2. Nitrogen, Sodium and Potassium Balance Data in Normal Premature Infant.

In top 3 graphs, total length of bar below zero line represents intake, clear area represents fecal excretion, vertical hatching urinary excretion, and solid black net positive balance. Negative balances project above base line and are indicated by diagonal hatching.

Bottom graph compares nitrogen and potassium balances. Normal proportion of these elements in protoplasm is about 2.7 mEq. k/gm. N[7]. In this graph, gm. N has been multiplied by 2.7 so that bars should be of equal length when all K and N retained are used to form normal protoplasm. Possible causes for discrepancy are discussed in text.

graphs for N, Na and K, respectively, show that negative balances during postnatal fasting period rapidly became positive with beginning of feedings. Bottom graph compares experimental potassium balances with theoretic balances calculated from nitrogen retention by known normal proportionality between these 2 elements in protoplasm.[7] N(gm.) $\times$ 2.7 = K(mEq.). Calculation indicates that a disproportionately large amount of K was apparently retained, usually about double amount needed for formation of new protoplasm as measured by nitrogen retention. On 1st and 2nd days of life, however, the reverse was found, and potassium balances were less than expected.

## DISCUSSION

The study indicates that the level of urinary formaldehydogenic steroid excretion did not change measurably during the first 10 days of life, but rose significantly over the

entire period of the study. Urinary steroid excretion is often taken as an index of the production of the parent steroids; the rise observed in this study may reflect an increase in adrenal activity with age in young infants. If this interpretation is correct, the period of rising excretion coincides with the period of rapid involution of the fetal zone; and it would therefore appear unlikely that the fetal cortex is an important source of formaldehydogenic corticosteroids.

There are, however, other possible causes for the observed increase. First, it may reflect the improvement in renal concentrating power which is known to occur at this time of life. Second, the type or degree of conjugation of the urinary steroids may vary in the early weeks of life. Steroids are normally excreted largely as glucuronides, sulfates and perhaps as unknown complexes. The effectiveness of the preliminary hydrolysis of these conjugates is directly reflected in the final determinations, and unfortunately no very satisfactory method of hydrolysis is available. Variations at this stage of the procedure could produce major differences in the measured steroid excretion, and this difficulty constitutes one of the major obstacles to accurate estimation of urinary corticosteroids.[8]

The influence of these interfering factors on the measurement of formaldehydogenic

CHART 2

URINARY EXCRETION OF CORTICOSTEROIDS BY YOUNG INFANTS

| | Investigator | Method | Subjects | Age | Weight | Urinary Corticosteroids mg./m²/24 hr. Infants | Urinary Corticosteroids mg./m²/24 hr. Adults | Infant/Adult Ratio |
|---|---|---|---|---|---|---|---|---|
| CHEMICAL METHODS | Klein[10] | Heard and Sobel[11,12] | 9 Prematures | 10 to 69 days | 1330 to 3125 gm. | 1.09 | 0.90* | 1.2* |
| | King and Mason[13] | Corcoran and Page[2] | 3 Prematures<br>4 Full term | Not stated<br>Not stated | Not stated<br>Not stated | 0.90† | 0.31† | 3 |
| | Day[14] | Talbot et al.[15] | 7 Infants | 3 days to 8 wk. | Not stated | 0.70‡ | 0.14*,‡ | 5* |
| | Matson and Longwell[16] | Heard et al.[17] | 8 Prematures<br>4 Full term | 3 to 33 days | 2041 to 3473 gm. | 1.80§ | 0.82§ | 2.2 |
| | Read, Venning and Ripstein[18] | Daughaday et al.[19] | 10 Infants | 1 to 9 days | Not stated | 0.12 to 0.63 | 0.29 to 0.49 | 1 |
| | Lanman | Corcoran and Page[2] | 7 Prematures | 1 to 10 days | 1500 to 2100 gm. | 1.00 | 0.87 | 1.2 |
| | | | 8 Prematures | 1 to 64 days | 830 to 2780 gm. | 1.48 | 0.87 | 1.7 |
| BIOASSAY | Venning, Randall and György[20] | Venning and Kazmin[21] | 7 Prematures<br>12 Full term | 3 to 37 days | Not stated<br>Not stated | 0.055** | 0.035** | 1.6 |

* Investigator gave no adult value; figure taken from reference under "Methods."

† Author's mean value=0.18 mg./day in infants, 0.52 mg./day in adults. Present investigator estimates surface area at 0.2 m² in infants in 1.7 m² in adults.

‡ Author's mean value=0.14 mg./day in 3.2 kg. infant. Adult value of 0.24 mg./day taken from reference 15. Present investigator estimates surface area at 0.2 m² for infant, 1.7 m² for adults.

§ Author's mean values: 0.12 mg./kg./day in infants, 0.02 mg./kg./day in adults. Present investigator made calculations for a 3000 gm. infant with 0.2 m² surface area and 70 kg. adult with 1.7 m² surface area.

** Author's average values: 0.011 mg./24 hr. for infants, 0.060 mg./24 hr. in adult males. Present investigator estimates surface area of 0.2 m² in infants, 1.7 m² in adults.

steroids in this study cannot be accurately determined, and the interpretation that rising values reflect increasing adrenal activity during the time of fetal zone involution is subject to reservations imposed by these obstacles.

The study revealed no measurable difference between neonatal and adult values for urinary formaldehydogenic steroid excretion/unit of surface area. Various other bases for comparison may be used. Norval and King[9] have developed several functions of weight and height by which excretion does not change with age. Direct comparison by body weight, on the other hand, would cause infant values to exceed those of adults. Selection of a basis for comparison must remain arbitrary until more is known of the function of these hormones. In the meantime, surface area appears to be a logical choice, since it is an index of metabolism as a whole.

Various other investigators using a variety of methods have also measured corticosteroid excretion in young infants. The writer has compared (chart 2) the average infant values in each study with adult values obtained by the same method, where possible by the same investigator. The comparison of these averaged values can be criticized because of the small number of determinations in each study, the lack of uniformity for the ages of the infants observed, and the errors in estimating surface area when the data supplied were inadequate for this purpose. However, these are the only data at present known to the writer by which infant and adult corticosteroid excretion can be compared. The calculated ratios of infant and adult values in the various studies were found to be in reasonable agreement. The infants excreted from 1 to 5 times as much corticosteroid/unit surface area as did adults, and in no study did their averaged value fall below that of adults; but the statistical significance of these ratios cannot be easily tested. The data do not show whether adrenal function in the infant is adequate for his particular needs, since there is no measure of the demand for steroid in the organism.

The electrolyte and nitrogen balance studies are of interest chiefly in that they reveal a discrepancy between the balances of K and N. Potassium balances were usually about double the amount theoretically needed for protoplasm formation as calculated from the nitrogen retention. A possible cause for the discrepancy was suggested by Gamble and co-workers;[22] their calculations showed that unmeasured skin losses of Na, Cl and K in a one month old infant were equal to about half the positive balances experimentally determined by the usual measurements of dietary, urinary and fecal electrolytes. Correction of the positive balances by subtraction of these unmeasured skin losses would therefore reduce the net retentions by about one-half, and the potassium balances would then be comparable to the retentions of N, for which skin losses are negligible. This explanation accounts for the usually excessive apparent retention of K observed in the present study. During the first two days of life, however, this excessive retention of K as compared to N was not demonstrated; instead, there was a relatively excessive loss of K, and the inclusion of unmeasured additional skin losses of K would only increase the discrepancy. A similar early excessive loss of K relative to N was found in premature infants by Smith and co-workers,[23] who postulated an endocrine basis, possibly adrenal, for this finding. The early excessive loss of K would be consistent either with transient adrenal cortical overactivity or with recovery from a hypoadrenal state. The present study gives no indication of either, since no sharp change in adrenal function was found in the first days of life. Such a change occurring at the moment of birth could not, however, have been detected by the methods used. It is also possible for the electrolyte regulating factor to vary independently of other adrenal functions.

A disproportionate loss of intracellular K relative to N is known to occur in several situations,[24] including acidosis,[25] alkalosis[26] and inanition;[27] in general, many unfavorable influences on the cell may impair its ability to maintain the high concentration gradient for K across its membrane. The period of inanition following birth, or perhaps other unfavorable conditions occasioned by the suddenly imposed demands of an independent existence may be responsible for the neonatal excessive loss of K relative to N. The influence of inanition is of particular interest since it is correctable and since the peculiarly unfavorable position of the newborn infant as regards available metabolites has received scant attention.[28]

## Summary and Conclusions

Urinary formaldehydogenic steroid excretions were measured in eight premature infants without recognized disease for varying periods up to 2 months of age. A balance study for Na, K and N was carried out in one infant.

Urinary formaldehydogenic steroid excretion did not change measurably during the first 10 days of life, and was not significantly different from adult normal values when compared on a surface area basis. Calculations from the data of other investigators indicate that infant values are from 1 to 5 times those of adults when compared by surface area.

Urinary formaldehydogenic steroid excretions rose significantly with age when the entire period of study for all infants was included. This rise occurred during the period of fetal cortical involution and is evidence that the fetal zone is not an important source of formaldehydogenic steroids.

The nitrogen and electrolyte balance study revealed a loss of K in the first 2 days of life which was disproportionately greater than the loss of N during the postnatal fasting period. The formaldehydogenic steroid excretion did not change measurably at this time, so that the study does not support the concept of changed adrenal function as a cause for this K/N disproportion. The electrolyte-regulating hormones can, however, vary independently of other adrenal functions. Acute inanition in the neonatal period of fasting is suggested as a possible cause for the disproportion.

## Acknowledgment

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SPANISH ABSTRACT

## Función Cortical de las Suprarrenales en Niños Prematuros

### 1. Niños sin Enfermedad Reconocida

Con objeto de determinar si la zona fetal de las cápsulas suprarrenales, cuyo desarrollo es prominente durante la vida intrauterina pero que involuciona y finalmente desaparece después del nacimiento, es capaz de producir corticoesteroides, el autor del artículo realizó la medición de la excreción de esteroides formaldehidogénicos urinarios en ocho niños prematuros sin enfermedad que pudiera ser reconocida, por periodos variables hasta la edad de dos meses, completando la investigación haciendo un estudio de balance para el Na, K y N en uno de los niños. Las conclusiones

a que llega el autor son las siguientes; (1) La excreción de esteroides formaldehidogénicos urinarios no cambio en forma mesurable durante los diez primeros dias de la vida y no fué diferente significativamente de los valores del adulto cuando se comparó sobre la base de la superficie corporal. Los cálculos de los datos de otros investigadores indica que los valores del niño son de 1 a 5 veces los del adulto cuando se comparan sobre la superficie corporal, (2). La excreción de los esteroides formaldehidogénicos urinarios se elevó significativamente con la edad cuando se incluyó el período entero de estudio de todos los niños. Esta elevación ocurrió durante el periódo de involución de la corteza fetal y es una prueba de que la zona fetal no es una fuente importante de esteroides formaldehidogénicos. (3) El estudio de balance nitrogenado y electrolítico reveló una pérdida de K durante los primeros dos días de la vida que fué desproporcionalmente mas grande que la pérdida de N durante el período de ayuno postnatal. La excreción de esteroides formaldehidogénicos no varió en forma medible en este tiempo de manera que el estudio no sostiene el concepto de un cambio en la función suprarrenal como causa de esta desproporción entre el K y el N. Las hormonas reguladoras de los electrolitos, sin embargo, pueden variar independientemente de otras funciones suprarrenales. Se sugiere que la posible causa de dicha desproporción sea la inanición aguda del periódo neonatal de ayuno.

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# ALYMPHOCYTOSIS

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THE study of a child with an apparent blood dyscrasia which terminated fatally at The Hospital for Sick Children and in which the pre-eminent feature at postmortem was an extreme atrophy of lymphoid tissue prompted a survey of the literature for similar cases. Only one report concerning two cases almost identical with the present one was uncovered.

Hypoplastic or depressed states of the various parent tissues of the cellular components of the blood, either idiopathic or due to a known cause, have long been recognized. The clinical syndromes, the findings in the peripheral blood, the bone marrow observations, and the postmortem changes have been frequently described. These blood dyscrasias have been classified, and a wide variety of names have been appended, depending upon the cell type involved, concept of pathogenesis, and as to whether an etiologic factor was known. These hypoplastic states occurring either singly or in combination involve chiefly the erythroid, the granulocytic and the megakaryocytic-platelet groups of cells. As far as can be ascertained no case has been reported where the reticulo-endothelial-monocyte system was primarily involved. Although the depressing effects of ionizing radiation, chronic illness, stress, and the hormones ACTH and cortisone on the lymphoid apparatus are well known, apparent spontaneous regression of lymphoid tissue must be exceedingly rare.

Glanzmann and Riniker[1] under the term "essential lymphocytophthisis" describe two fatal cases occurring in young infants, a female aged 5½ months and a male aged 6 months. In each of these patients there was widespread involvement of the alimentary tract and lungs with Candida albicans (monilia) associated with a progressive lymphycytopenia and a terminal pancytopenia. The post mortem in each case revealed almost complete depresion or atrophy of lymphoid tissue throughout the body. The authors discuss at length the implications of this unusual syndrome which they feel probably represents a clinical entity. They point out that infection with monilia is not common in their hospital and although the blood picture might possibly be due to the infection with the fungus, they do not believe that such is the case. They favour the concept that primarily there was a constitutional defect and that although there was a general myelophthisis the hypoplasia or atrophy of the lymphoid apparatus was the outstanding feature.

The following case follows closely the syndrome described by Glanzmann and Riniker. It is apparently the third to be reported and the first in the American literature. The author has preferred to designate the symptom complex "alymphocytosis" rather than "essential lymphocytophthisis," not because the former has any fundamental merit but for the purpose of drawing attention to the striking lymphocytopenia and because alymphocytosis is more analogous to the terms aplastic anaemia and agranulocytosis, which are common usage.

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## Case Report

C. B., a white male 2 11/12 yr. of age, was admitted to The Hospital for Sick Children, with a history of fever, weight loss, weakness and anorexia of 3 wk.' duration.

Family background, birth, feeding, environmental and developmental history were not unusual. He had received diphtheria toxoid and pertussis vaccine. The only past illness of note was a "febrile convulsion" at age of 7 mo.

Patient suffered 6 mo. previously from acute tonsillitis which was successfully treated at home with penicillin and a "sulpha preparation." Two months later a recheck revealed chronically inflamed tonsils. However, he was well until 3 wk. prior to admission at which time he developed foul breath, anorexia and a fever of 40.0°C.

For 3 wk. preceding admission he was treated at home as a case of tonsillitis with a triple sulpha preparation (approximately 10 gm.) and 2 injections of penicillin. Throughout this period, a nocturnal pyrexia persisted and he continued to refuse solid foods and lost weight. Three days before admission he excreted only a small amount of dark reddish urine. When the parents brought the patient to the hospital, an investigation revealed an hepatosplenomegaly with a WBC count of 800/cmm.

Physical examination revealed on admission temperature of 40.0°C., PR 150/min. and resp./40 min.—a chronically ill child with a pale hot skin. Tongue was moist and coated with a white adherent scum. Tonsils were moderately enlarged and acutely inflamed. Liver extended to level of umbilicus. It had a smooth surface and a soft regular edge. Spleen was palpable 8 to 10 cm. below costal margin. It was firmer than the liver but appeared to be of normal outline.

Laboratory Findings: Hgb. 9.2 gm./100 cc. blood, WBC count 1.1 thousand/cmm. Differential: granulocytes 92% (40% bands, 50% segmented, 2% eosinophils), lymphocytes 8%. Platelets 280 thousand/cmm. Reticulocytes 0.3%. Sternal marrow aspiration, megakaryocytes scanty; differential granulocytes 29% (myelocytes 4%, metamyelocytes 4%, bands 16%, segmented 2%, eosinophils 3%), lymphocytes 18%, monocytes 4%, erythroid 49%. Fragility test normal. Coombs test negative. Serum albumen 2.55 gm./100 cc., serum globulin 2.40 gm./100 cc. Van den Bergh direct .64 mg./100 cc., indirect .67 mg./100 cc. Cephalin flocculation test negative. No auto- or isoagglutinins present at 4°C., 20°C. and 37°C. Blood culture negative. Agglutination for S. typhi H and O, S. paratyphi, A and B, and Br. abortus negative on 3 occasions. Heterophile antibody test negative. Culture of marrow negative for bacteria, fungi and yeasts. Throat swab positive for Ps. aeruginosa (pyocyaneus) which was resistant to all antibiotics except polymixin.® Tuberculin skin test negative to 1/2000 mg. Histoplasmin skin test negative to 1/100 mg. Wassermann test negative.

Course: Hematologic observations are detailed in tables 1 and 2. Following admission, therapy with penicillin was instituted and continued for 6 days. During this time there was no significant change from his general condition on admission. Temperature continued to rise to as high as

TABLE 1

Hematologic Data—Peripheral Blood (C.B., male, 2¾ yr.)

| Date—November 1951 | 9 | 10 | 12 | 15 | 16 | 18 | 20 | 21 | 22 | 25 | 26 | 27 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin as gm. 100 cc. blood | | 9.2 | | 7.3 | | 8.9 | 10.9 | 9.2 | 9.2 | 8.2 | 8.4 | 10.2 | 9.7 | 7.5 |
| Transfusions in cc. | | | | | 250 | 250 | 250 | | | | | | | |
| WBC count as $10^3$/cmm. | 0.8 | 1.1 | | 1.6 | 2.5 | 1.3 | 1.2 | 0.8 | 1.5 | 1.5 | 1.8 | 1.4 | 0.5 | 0.4 |
| Platelets as $10^3$/cmm. | | 280 | 280 | | | | | | | | | | | |
| Reticulocytes % | | | | 0.3 | | | | | | | 2.0 | | | |
| Fragility | | | | | normal | | | | | | | | | |
| Peripheral Differential in % | | | | | | | | | | | | | | |
| Bands | | 40 | | 43 | | | | | | | 32 | | | |
| Segmented | | 50 | | 44 | | | | | | | 56 | | | |
| LYMPHOCYTES | | 8 | | 4 | | | | | | | 4 | | | |
| Monocytes | | 0 | | 9 | | | | | | | 8 | | | |
| Eosinophils | | 2 | | 0 | | | | | | | 0 | | | |

TABLE 2

HEMATOLOGIC DATA—BONE MARROW (C.B., male, 2¾ yr.)

| Date—November 1951 | 9 | 10 | 12 | 15 | 16 | 18 | 20 | 21 | 22 | 25 | 26 | 27 | 28 | 29 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total nucleated count $10^3$/cmm. | | 100 | | | | | 25 | | | | | | | * |
| Megakaryocytes/cmm. | | 22 | | | | | 0 | | | | | | | — |
| Differential in % | | | | | | | | | | | | | | — |
| Myelocytes | | 4 | | | | | 10 | | | | | | | 15 |
| Metamyelocytes | | 4 | | | | | 10 | | | | | | | 12 |
| Bands | | 16 | | | | | 42 | | | | | | | 33 |
| Segmented | | 2 | | | | | 10 | | | | | | | 3 |
| Eosinophils | | 3 | | | | | 0 | | | | | | | 5 |
| LYMPHOCYTES | | 18 | | | | | 2 | | | | | | | 11 |
| Monocytes | | 4 | | | | | 2 | | | | | | | 2 |
| Erythroid | | 49 | | | | | 28 | | | | | | | 12 |

* Performed immediately after death.

40.5°C., following normal levels the same day. Aspirin had no effect on fever. Gradually throat became more inflamed, a mild stomatitis developed and lips began to fissure and bleed. A culture taken from mouth at this time showed no significant organism. Treatment with chloromycetin® in addition to penicillin was begun on 6th hospital day without apparent effect. On 8th and again on 9th hospital day he was transfused with whole blood 250 cc. Hemoglobin rose slightly but WBC count remained low. On 9th day his condition considerably deteriorated. His face became oedematous, abdomen distended, grunting respiration developed and he vomited dark brown material. At this juncture penicillin was stopped and replaced by streptomycin. Symptomatic and antibiotic therapy were without apparent effect. Patient was taking very little food by mouth. Another transfusion of blood 250 cc. was given on 11th day. On 14th day, he developed a harsh cough and a husky voice which was relieved by steam inhalations. On 17th day he developed a severe thrush-like stomatitis which apparently improved slightly with local treatment. Cultures from this lesion grew Ps. aeruginosa (pyocyaneus). Although liver remained below umbilicus, spleen seemed to be smaller than originally but was still readily palpable. Temperature continued to be elevated. On 19th day he began to have frequent loose brown stools and his general condition considerably worsened. His temperature continued in the neighbourhood of 39.4°C. and respirations were rapid and gasping. RG chest plate at this time was negative. Following day patient lapsed into semiconsciousness and died shortly thereafter, 20 days after admission.

Salient clinical features of the case were an apparent blood dyscrasia characterized by enlargement of liver and spleen and a leucopenia with an absolute reduction of all types of leucocytes but particularly deficient in lymphocytes. Marrow studies showed moderate activity of both granulocytic and erythroid elements with initially a low normal lymphocyte count which subsequently definitely fell to abnormal levels. Continued fever was considered to be evidence of an infection secondary to the blood abnormalities by organisms which were opportunists, resistant to antibiotics and ordinarily low grade pathogens. However, the possibility of an obscure specific infection resulting in the unusual hematologic findings was not entirely discounted. Thrush-like lesions of mouth were noted during life but the apparent pyocyaneous infection caused more concern.

POST MORTEM, A.281/51.

Gross Examination: Performed 2 hr. after death. External appearance of body was not striking. Usual pallor was somewhat accentuated. Liver and spleen could be palpated through the abdominal wall. There were no excoriations or ulceration of lips and buccal cavity. Crypts of tonsils contained a white exudate but no gross areas of ulceration were detected.

Larynx and trachea were not unusual. Bronchi contained a small amount of brownish mucus and lungs showed a few small patchy areas of hemorrhagic consolidation.

Thymus was pale, thin and soft, weighing only 6 gm.

Oesophagus was the site of an extensive lesion beginning approximately 3 cm. below the cricoid. Mucosa of the lower ⅔rds of oesophagus was completely covered with a thick rugose whitish friable membrane. This membrane became progressively thicker as the distal end of oesophagus was approached. At the cardiac orifice this membrane measured up to 0.5 cm. in thickness and had almost completely occluded the lumen. Membrane terminated abruptly at the cardiac orifice and did not extend to mucosa of the stomach. Smear and culture of this membrane revealed abundance of C. albicans (monilia). Remainder of the alimentary tract was distended with gas but mucosa was smooth and intact with the exception of the rectum which at a point 5 cm. proximal to mucocutaneous junction contained a shallow mucosal ulcer 3 mm. in diameter. Solitary lymph follicles and Peyer's patches were not discernible.

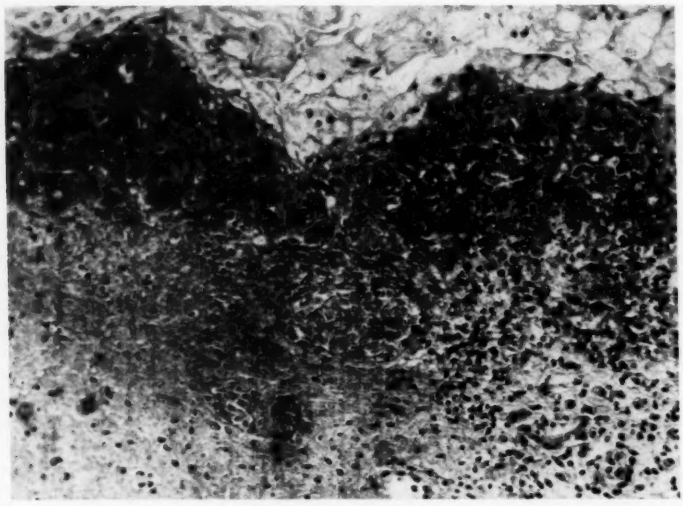


FIG. 1. Tonsil. Epithelium at top of photomicrograph is degenerating but intact. Viable tissue at right is almost devoid of lymphocytes. Tissue at left is necrotic. × 211.

Liver (weight, 1023 gm.) was of normal shape but more than twice normal size (normal weight approximately 400 gm.). External surface was smooth and pale brown. Its consistency was soft. Aside from its pallor cut surface showed no characteristic features.

Spleen (weight, 131 gm.) was enlarged (normal weight approximately 35 gm.). Its configuration, capsular surface, and colour were normal. Cut surface was dark red and exuded an excessive amount of blood. Malpighian bodies were not discernible. Cervical, thoracic and abdominal lymph nodes were slightly enlarged, pale and soft. Unfortunately lymphoid tissues in other areas of the body were not examined.

Bone marrow of sternum, ribs and lumbar vertebrae appeared normal. Remainder of the organs and tissues throughout the body including an examination of cranial contents were normal.

Microscopic Examination: Histologic appearances of thyroid, submaxillary gland, heart, pancreas, adrenal, kidney, urinary bladder, testis, pituitary, and brain were within normal limits. Trachea was normal with no evidence of monilia infection.

Examination of one tonsil revealed major portion of tissue to be completely necrotic although epithelium over most of the organs was intact (Fig. 1). In necrotic areas were large numbers of bacteria but no fungus. Between necrotic areas were small islands of preserved tissue which presented an appearance identical with that seen elsewhere in the lymphoid tissue and which is described below.

Lungs showed a few small patches of nonspecific hemorrhagic bronchopneumonia due to terminal aspiration of food and/or vomitus. In areas involved large numbers of bacteria were present with a

FIG. 2. Mycelia of C. albicans invading epithelium of oesophagus. × 648.

very scanty inflammatory reaction composed of polymorphonuclear and mononuclear cells. No fungus was discernible.

Oesophagus, particularly in its lower part, showed extensive confluent areas of ulceration. Ulcerated areas were covered with a thick layer of necrotic debris in which were innumerable typical mycelial threads and spores of C. albicans (monilia) (Fig. 2). Islands of partially necrotic epithelium were likewise infiltrated with the mycelia. The fungus had penetrated to the superficial muscle layers. Although ulceration was extensive the inflammatory reaction was minimal and extended only a short distance into the underlying muscle. The inflammatory cells were polymorphs and mononuclears in about equal proportions. The ulcer in the rectum was shallow with some

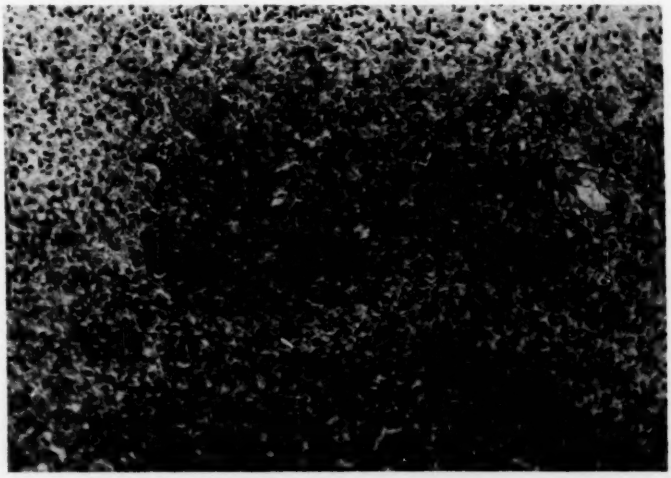


FIG. 3. Complete disappearance of malpighian corpuscle in spleen of C. B. Central follicular arteriole is approximately in center of photomicrograph. Compare with Fig. 4. × 200.

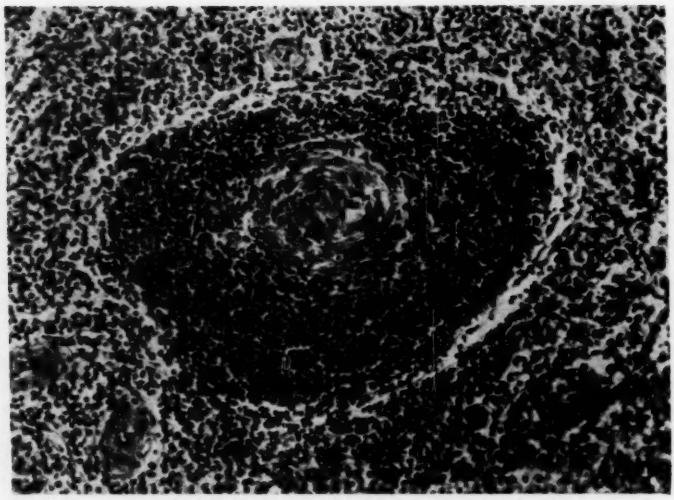


FIG. 4. Malpighian corpuscle in spleen of child of same age and sex as C. B. who died with nephrotic syndrome. Same magnification as Fig. 2. × 200.

fibrosis of the floor. The surrounding inflammatory reaction was composed almost entirely of mononuclears with only an occasional polymorph. There was no fungus. Sections of the stomach, duodenum, jejunum, ileum and colon showed no ulcerations but the lymphoid tissue in the mucosa was entirely lacking except for a few widely spaced small foci of 10 to 20 lymphocytes in some of the Peyer's patches. Changes in the lymphoid structures of the gut were identical with those described below in lymph glands.

The most striking feature in the spleen was complete absence of lymphocytes in the malpighian corpuscles (Figs. 3 and 4). In areas of the defunct malpighian bodies there was much karyorrhexis and nuclear debris (Fig. 5). Most of this material had been phagocytized by cells of the reticulo-

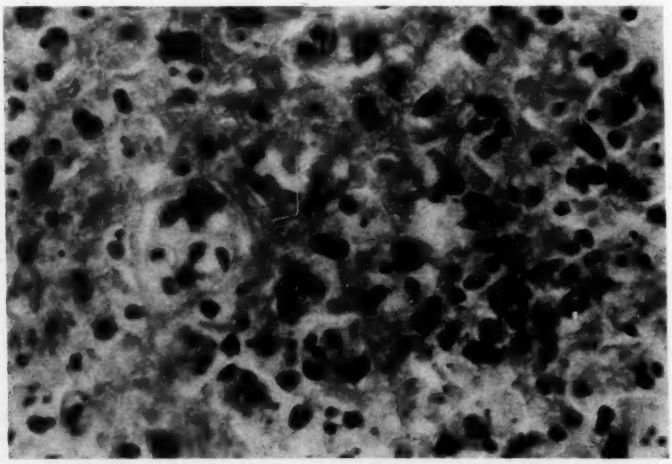
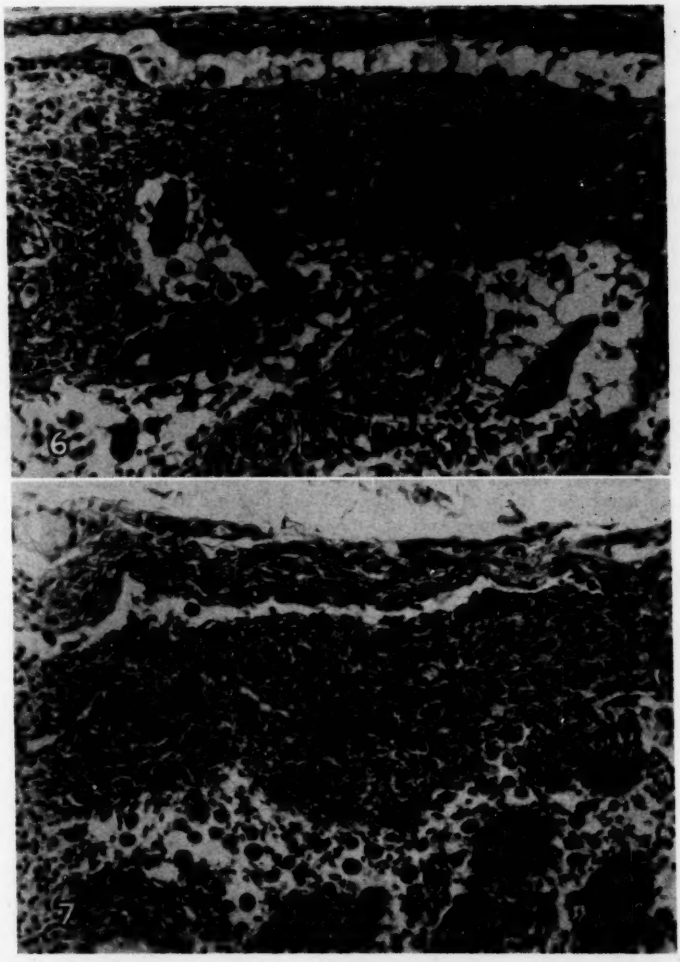


FIG. 5. Higher magnification of malpighian corpuscle in spleen showing lysis of lymphoid tissue and phagocytosis of nuclear debris by cells of reticuloendothelial system. × 576.



FIGS. 6 and 7. Cervical and mesenteric lymph glands, respectively, illustrating disappearance of lymphoid tissue. Tissue is composed of collapsed stroma and reticuloendothelial elements with no lymphocytes. In sinusoids are many phagocytes. × 200.

endothelial system. Similar cells showing erythrophagocytosis were numerous in the pulp spaces. The tissue was congested but there was no significant fibrosis, hematopoiesis or siderosis.

Cervical, peribronchial, peripancreatic, periaortic and mesenteric lymph glands were available for study. These all presented the same unusual picture. The glands were almost entirely devoid of lymphocytes (Figs. 6 and 7). This imparted a peculiar "sponge-like" appearance to the tissue. There was condensation of the connective tissue capsule due to some total shrinkage of the glands. Reticulum stain revealed the connective tissue stroma and reticulum to be intact but considerably compacted. Blood and lymph sinuses were prominent. In widely scattered areas there were clumps of a few lymphocytes. There seemed to be proliferation and marked activity of the reticuloendothelial elements but this might in part be due to unmasking as a result of the lack of lymphocytes. Throughout the nodes there was much nuclear debris particularly in the areas formerly occupied

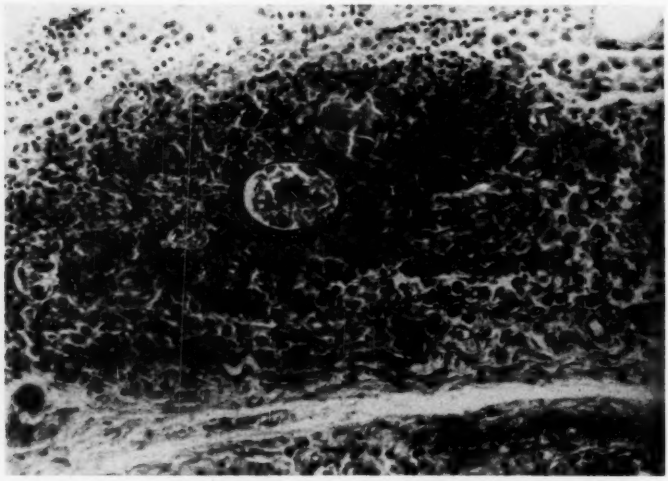


FIG. 8. Thymus. In center is Hassal's corpuscle. Although there are few aggregations of lymphocytes, disappearance of lymphoid tissue is striking.

by the lymph follicles. Phagocytosis of the nuclear debris and red blood cells was a prominent feature. The erythrophagocytosis must have been a relatively late phenomenon as special stains revealed no appreciable amounts of iron pigment.

Thymus presented an appearance which in respect to lymphoid tissue was essentially similar to that seen in the lymph glands (Fig. 8).

The extreme enlargement of the liver was difficult to explain on a histologic basis. The organ was moderately congested. A few polymorphs were present in the blood within the sinusoids. There were no characteristic or specific changes in the liver cells. Kupffer cells which were not

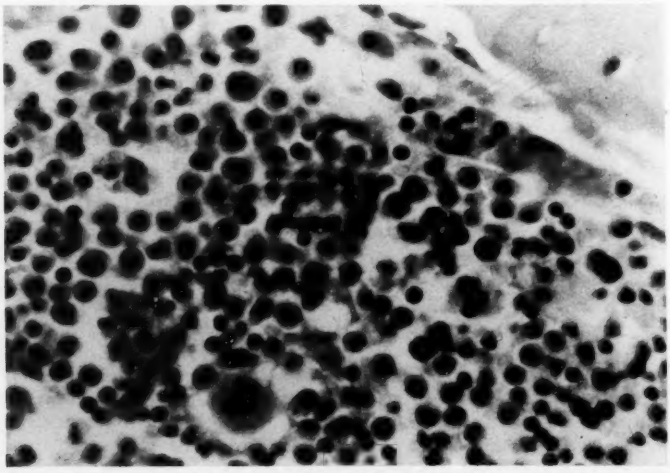


FIG. 9. Bone marrow of vertebra. It is difficult to distinguish with precision various cell types. Although cells are somewhat more loosely packed than usual, megakaryocytes, erythroid and granulocytic elements are well represented. × 600.

unduly prominent, contained a small amount of iron pigment. A few scattered areas of focal necrosis were present with little or no inflammatory reaction except phagocytosis of nuclear debris by mononuclear cells.

Bone marrow of the sternum, rib and vertebra was, for the most part, moderately hypoplastic. It appeared edematous and the blood sinusoids were prominent. Megakaryocytes, erythroid elements and granulocytes were present in considerable numbers and in the usual proportions, but few lymphocytes could be identified (Fig. 9). Within the sinusoids there were many large mononuclear cells with phagocyted nuclear debris and erythrocytes. In some localities, particularly the vertebra, the cellularity of the bone marrow was within normal limits. The bone structure was normal.

## Comment

This case is similar in all essential features to the two cases in infants described by Glanzmann and Riniker and seems to represent a clinical and pathologic entity. Before death the bizarre pattern of the blood picture in the case reported here was appreciated. The general clinical consensus at first was that an obscure infection was probably the primary cause, although a careful search for such an agent was not successful. The presence of the monilia infection of the oesophagus escaped detection. Hematologic investigation during life indicated that there was a depression of all cellular elements in the peripheral blood but the striking feature was an almost complete disappearance of the lymphocytes. Three bone marrow examinations indicated a fairly good response on the part of the erythroid and myeloid series throughout the course of the illness. In the first marrow aspiration, the lymphocyte count was in the low normal range. In the two later samples, the count was definitely below normal.

Treatment with ACTH and/or cortisone was withheld because it was considered that this would have been a dangerous procedure in the presence of an apparent severe infection; and the effects of these hormones on the hematopoietic and lymphoid tissue would probably have tended to aggravate the existing situation. Consequently the therapy employed was supportive and symptomatic with exploratory use of various antibiotics in an attempt to combat a possible unknown infection.

The postmortem finding of almost complete disappearance of all lymphoid tissue was confirmation of the clinical hematologic finding, but still inexplicable. This feature was most impressive. In children, particularly those with illnesses of some duration, atrophy of lymphoid tissue is usual but not to the degree seen in this child. The reticulum of the lymphoid apparatus was intact. Cells of the reticuloendothelial system were abundant and active as evidenced by the considerable degree of phagocytosis. These changes in the lymphoid apparatus are similar to those described by Jacobson et al.[2] in experimental animals following total body radiation. This remote possibility was considered in the present case but ruled out.

This boy's disease was well established when he was first seen. There was nothing in the history to indicate exposure to any peculiar drugs or chemicals. If the exhibition of sulphonamides and/or penicillin which were the only drugs he had received prior to admission could have resulted in such a clinical and hematologic picture, this effect must be exceedingly rare. A peculiar idiosyncracy to sulphonamides can probably be eliminated inasmuch as these drugs were not used in the two cases described by Glanzmann and Riniker. The possible myelotoxic effect of chloromycetin® cannot be implicated as this was not given until his 6th hospital day.

Infection may have played a part as a trigger mechanism in this boy, initiating the process in a lymphoid apparatus and bone marrow with a peculiar constitutional defect. However, to incriminate infection as the only causative factor, one would have to

postulate a rare type of infection resistant to the ordinary antibiotic and evoking an unusual type of tissue response. It might be considered that the treatment with sulphonamides and antibiotics precluded the possibility of isolating specific causative organisms. This hardly seems likely, as there was at no time any evidence of an abatement of the disease process which should have occurred if the therapy had any significant bacteriostatic or bacteriocidal effect on an etiologic agent.

The role of the infection with C. albicans (monilia) is difficult to assess. This was a common factor in this case and the two described by Glanzmann and Riniker. Most authorities consider monilia to be only a facultative pathogen. Antibiotics, particularly penicillin, were used in all three cases. The association of moniliasis with antibiotic therapy has been stressed in the recent literature. It is possible that the antibiotics enhanced the growth of this fungus by altering the flora of the alimentary tract. Moniliasis is seen not infrequently, particularly in recent years, as a terminal complication in leukemia. It is usually considered that this is not due to any increased virulence of the fungus but merely because the patients are being kept alive longer with various forms of specific and nonspecific therapy including the antibiotics. Eventually in these leukemic patients there is a complete lack of humoral and cellular resistance to infection and the patients finally succumb to a relatively avirulent infection against which no protection is available.

Although it cannot be entirely discounted it is considered unlikely that the monilia infection was primary and that the fungus elaborated a toxin which resulted in almost complete lysis of the lymphoid tissue. A more plausible explanation is that for some unexplained reason there was a depression of the various blood elements which in this case particularly affected the lymphoid apparatus and the resultant disturbance of the cellular and humoral resistance of the body prepared the soil for the implantation of a relative avirulent organism. The low serum albumen is difficult to explain. It may possibly be an index of the humoral changes.

Although the agent or deficiency that resulted in the disappearance of the lymphoid tissue was not entirely selective as there was evidence of a depression of the other cellular elements of the blood, nevertheless, the changes affecting the lymphoid apparatus were sufficiently striking in this boy to set it apart from the usual case of aplastic anaemia or agranulocytosis.

## Summary

This study describes an unusual fatal disease in a child, which was characterized by fever, hepatomegaly, splenomegaly and a leucopenia in which the striking feature was a lymphocytopenia.

Postmortem examination revealed a widespread "idiopathic" atrophy and necrosis of the lymphoid tissue. An associated finding was an extensive monilia infection of the oesophagus.

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## Spanish Abstract

### Alinfocitosis

El autor relata un caso fatal de discrasia sanguínea cuyas características prominente al estudio postmortem fué la atrofia extrema del tejido linfoide.

Por mucho tiempo han sido reconocidos los estados de hipoplasia de varios tejidos paternos de

los componentes celulares de la sangre, ya idiopáticas, o de causa conocida y cuyos síndromes clínicos, cuadros hematológicos y cambios postmortem han sido descritos con frecuencia, designándose y clasificándose de acuerdo con el tipo de célula afectado, patogenesis y etiologia. Estos cuadros hipoplásticos ocurren ya aisladamente o en combinación afectando las células eritroides, granulocíticas y el grupo megacariotrombocitario. Solo existen 2 casos reportados en la literatura que son casi idénticos con el del autor, descritos con el nombre de linfocitosis esencial por Glanzmann y Riniker. Se trató de dos casos fatales en lactantes de 5½ y 6 meses, de sexo femenino y masculino respectivamente, en los cuales había un ataque difuso por cándida albicans (monilia) del aparato digestivo y pulmones, asociado con linfocitopenia progresiva, pancitopenia terminal y depresión completa o atrofia generalizada del tejido linfoide. Los autores pensaron que se trataba de un defecto constitucional y que aunque había mieloptisis general la hipoplasia o atrofia del aparato linfoide era característica principal.

El caso del autor es el de un niño de 2 años 4 meses que durante 3 semanas tenía fiebre, debilidad, anorexia y adelgazamiento. Varios meses antes de su admisión tuvo 2 episodios de amigdalitis aguda tratadas con penicilina y sulfa y sus amígdalas se consideraron crónicamente inflamadas. Sin embargo, estuvo bien durante los 4 meses previos a su enfermedad. Esta se trato en casa con sulfas y penicilina. La exploración reveló un niño febril, enfermo crónicamente y palído, con amígdalas moderadamente hipertrofiadas con inflamación aguda. Hígado a nivel del ombligo, de superficie lisa y borde blando regular, bazo a 8-10 cm. abajo del reborde costal, de mayor consistencia que el hígado, de límites normales.

Se hicieron investigaciones bacteriológicas extensas para encontrar la causa de la fiebre resultando negativas. Los datos de laboratorio importantes se hallaron en sangre que mostraba leucopenia, 2.500 elementos con mínimo de 400 antes de morir, con 83 a 92% de granulocitos y de 4 a 8% de linfocitos. Los mielogramas demostraron de 2 a 18% de linfocitos. El enfermo se trató con penicilina, cloromicetina y estreptomicina, sin lograr abatir la fiebre. Desarrolló sucesivamente estomatitis ligera, edema, meteorismo, respiración ruidosa, vómitos de material obscuro, tos cavernosa y ronquera. La estomatitis se hizo severa y adquirió el tipo de la del algodoncillo encontrándose bacilo piocíanico en los cultivos. El día anterior de su muerte tuvo diarrea con evacuaciones negras, disnea, falleciendo en estado semi-inconciente a los 20 días de internarse.

Al estudio postmortem macroscópicamente se encontró como hallazgos importantes: esófago en sus ⅔ inferiores cubierto de una membrana, friable, blancuzca, cuyos frotis y cultivos revelaron abundancia de candida albicans (monilia); una úlcera poco profunda de 3 mm. de diámetro y las placas de Peyer y los folículos linfáticos solitarios, no eran perceptibles. Hepatomegalia y esplenomegalia con ausencia de cuerpos de Malpighi. Los ganglios linfáticos cervicales torácicos y abdominales ligeramente agrandados pálidos y blandos. Al examen microscópico areas ulcerosas esofágicas cubiertas de micelios y esporas de monilia con fenómenos inflamatorios mínimos, pequeñas zonas de reacción bronconeumónica terminal no específica, con gran cantidad de bacterias pero escasa reacción inflamatoria de polimorfonucleares y mononucleares. Lo que era sorprendente fué la ausencia completa de tejido linfático en la mucosa del estomago, duodeno, yeyuno, ileon y colon excepto por pequeños focos de escaso infiltrado linfocitario en algunas de las placas de Peyer; la ausencia de linfocitos en los corpusculos de Malpighi del bazo, substituidos por kariorrexis y restos nucleares, material que era en gran parte fagocitado por celulas reticuloendoteliales, igual fenómeno se observaba en la pulpa. Todo el tejido linfático de los ganglios, intestino y amigdaliano presentaba el mismo aspecto desusual, estaba desprovisto de linfocitos, dándole un aspecto como de esponja, el reticulo estaba intacto pero muy compacto, los sinusoides prominentes, había proliferación y actividad marcada de elementos reticulo-endoteliales. La médula ósea presentaba moderada hipoplasia, había un número considerable de megacariocitos, elementos eritroides y granulocitos, en sus proporciones normales, pero pocos linfocitos. En los sinusoides había numerosas células mononucleares grandes con restos nucleares y eritrocitos fagocitados.

El autor sintetiza los hallazgos postmortem diciendo que correspondieron a atrofia y necrosis difusa idiopática del tejido linfoide asociada a una extensa infección moniliásica del esófago.

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# TRANSIENT DIABETES IN INFANCY

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DIABETES mellitus is defined as "A syndrome characterized by hyperglycemia and glycosuria and associated with abnormal metabolism of fat and protein."[1] White reports 14 possible arrested cases of diabetes in childhood.[2] However, in edition 8 of the same text Joslin[3] says "We have searched zealously for cures and have not found them." Soderling questioned 100 clinic directors in 21 countries as to whether they had seen cures of true diabetes in young individuals. He could find only two reports where definitely proved diabetes was apparently cured.[4]

Fykow[5] reports the case of a 25 month old female who had a left lower lobe pneumonia and symptoms of diabetes mellitus. She was given insulin with marked improvement. When the pneumonia cleared, her sugar tolerance improved. Four months later she had a normal fasting blood sugar (92 mg./100 cc.) but had an abnormal glucose tolerance curve with blood sugar of 148 mg./100 cc. at the end of three hours. She had remained sugar-free on a general diet.

Schwartzman et al.[6] reported 57 cases of diabetes in infants under one year of age. A close inspection of these shows three in which a transient so-called diabetic state was followed by improvement and apparently complete cure of the diabetes. In two of these there was associated a severe infection which apparently precipitated the diabetic condition. After cure of the co-existent illness, the diabetic condition disappeared. The third case was associated with a respiratory infection but may have had symptoms antedating the upper respiratory infection.

The first case is that of Ramsey[7]; this was a full term male, birth weight 2200 gm., at 4 weeks—2085 gm. He developed signs of an upper respiratory infection, polydypsia, polyphagia and polyuria and was found to have glycosuria. He lost ground and was given insulin ½ unit (? how often) which made his urine sugar-free in four days. Blood sugar was 225 mg./100 cc. blood. He was discharged from the hospital in 6 weeks and remained sugar-free except when syrup was given 3 and 6 weeks later. At 7 months of age, the urine was free of sugar on a diet of whole milk, cereal, vegetables, orange juice and cod-liver oil. A glucose tolerance curve at 4 years of age gave the following results: fasting—60 mg./100 cc. blood; 1 hour, 95 mg.; 2 hours, 82 mg.; 2 hours, 77 mg.; 4 hours, 74 mg./100 cc. A recent communication from Dr. Frank Hedenstrom[8] states that now, 25 years later, the young man has remained healthy and has been accepted for military service.

Lawrence and McCance[9] report the case of an 18 day old female infant who had four bluish-black spots on the skin. Birth weight was 3.5 kg. She had been breast fed and did well until the 15th day of life when a black patch was noticed on the right wrist. On the 17th evening a similar spot was noted on the left ankle, and the following day two other discolored areas were noted. On admission, urine specimen showed a 4-plus positive test for sugar, but no acetone. Blood sugar the next day was 600 mg./100 cc. Insulin was

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given, 1 u. every 4 hours. With improvement this was then reduced and 5 days later was discontinued. The discoloration healed slowly in 11 weeks and the child was discharged as normal.

The third case, reported by Strandqvist,[10] is that of a full term female infant weighing 2200 gm. at birth (3/30/31). She developed a reddish swelling over the right shoulder, was feverish and seemed thirsty. Three days later the urine was positive for sugar and the blood sugar was 400 mg./100 cc. but no ketone bodies were found. She was given insulin up to 2 u. daily in divided doses. Two weeks later the glycosuria had been reduced to a point where further insulin was apparently not required. At the time of discharge, a glucose tolerance curve was normal.

Strandqvist's conclusion was "it seems more probable that the cause of the hyperglycemia and glycosuria is to be looked for in a toxic influence on the regulating centre of the carbohydrate metabolism in the brain, i.e., in the same way as the usual febrile hyperglycemia is explained."

### Case Report

G. W. (see Figs. 1 and 2) was an immature, white, male infant delivered spontaneously, wt. 2.2 kg., after a gestation of 9 mo. There was no known history of diabetes in any relatives.

He was given a formula of dried milk with 10% added sugar until 13th day when there was a precipitous weight loss unaccompanied by diarrhea or vomiting. On examination marked dehydration and poor turgor were noted. A diagnosis of adrenal insufficiency was suspected. He was given saline

Fig. 1. G. W., aged 18 days.
Fig. 2. G. W., aged 6 mo.

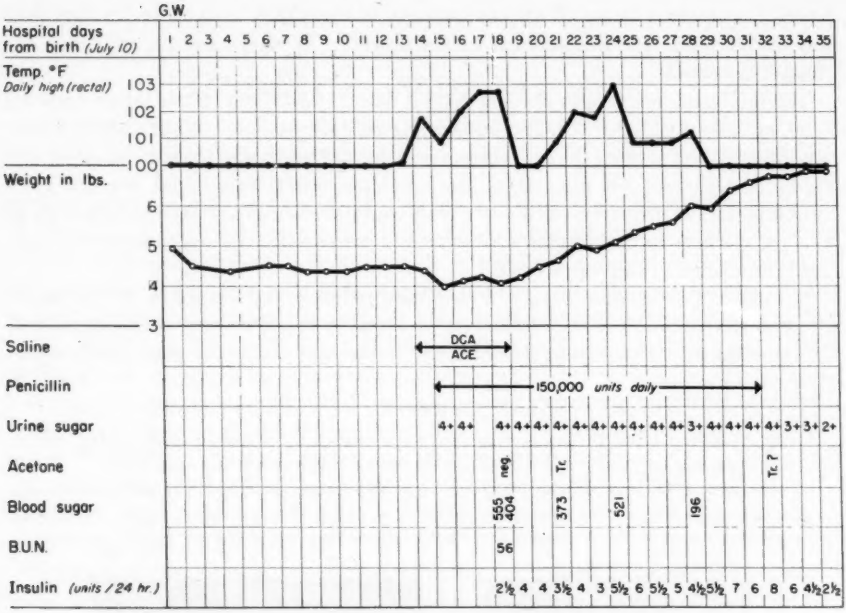


CHART 1

120 cc. intravenously and subcutaneously and desoxycorticosterone (DOCA ®) 1 mg. intravenously.

Progress was as follows (chart 1): Next day his condition seemed even worse. He was given saline 40 cc., whole blood 50 cc. intravenously and adrenal cortical extract (ACE) 10 cc. intramuscularly. Glycosuria was first noted on this day. The 15th day he received saline 120 cc., DOCA 1 mg. and ACE 8.0 cc. The 16th day he received saline 120 cc., DOCA 1 mg. and ACE 8.0 cc. The 17th day he received saline 80 cc., DOCA 1 mg. and ACE 8.0 cc. At this time fasting blood sugar was 555 mg./100 cc. and he was given regular insulin 2 u. followed by ½ u. every 6 hr. Insulin dosage varied from 2½ to 8 u. daily during hospitalization.

Laboratory data—13th day: Hgb. 16 gm./100 cc., RBC count 5.0 million/cmm., WBC count 8.7 thousand/cmm., PMN leucocytes 50%, lymphocytes 42%, monocytes 6% and eosinophils 2%. 14th day: urine—ph5, albumin faint trace, sugar 4+, 0 to 1 WBC/hpf. 15th day: urine—ph5, sp. gr. 1.034, albumin +, sugar 4+, casts 0, RBC 0 and WBC 0. Urinary sugar was identified as glucose.

Fever continued to 18th day when it abated for about 48 hr. Following this, there was a daily elevation of temperature until 38th day. Liver edge was noted to be 2 fingers below costal margin on 20th day and remained so at time of discharge. A mild pharyngitis appeared to be the only explanation for fever; no blood culture was made.

Following administration of insulin there was a dramatic improvement in infant's condition. He began to gain weight steadily. There was a continued glycosuria but never any untoward reaction to insulin. He was discharged on the 34th day weighing 3.1 kg. Mother was instructed to give him insulin 2½ u. daily.

On 44th day he weighed 3.8 kg. and was receiving regular insulin 3½ to 4½ u. daily. At this time he was changed to NPH insulin, u. 2, once daily. This was continued for 1 wk. when it was reduced to 1 u. daily. This was given for only 24 hr. when it was reduced to ½ u. daily. At about 2 mo. of age, insulin was discontinued. His urine has remained free of sugar since that time.

Development has been normal for his age. At 5 mo. of age he weighed 6.9 kg. and was 66 cm. tall. He was taking evaporated milk with 5% added sugar, together with cereal, fruit, meat and vegetables. There has been no return of fever and no glycosuria.

Glucose tolerance test, giving glucose 1.6 gm./kg. 2 mo. after onset (micro-method sugar)—fasting: 83 mg./100 cc.; ½ hr., 97 mg.; 1 hr., 110 mg.; 2 hr., 88 mg.; 3 hr., 90 mg.

## Discussion

An example of a diabetic-like state in infants is reported. Here, as in the description of four others from the literature, there had been an accompanying illness. When the pre-existent or coexistent illness had subsided, glycosuria and other metabolic disturbances have disappeared. In three of these five babies, in spite of the presence of marked glycosuria and an elevated level of blood sugar, little or no acetone or diacetic acid was found in the urine. In Ramsey's case, no mention was made as to whether acetone or diacetic acid was present in the urine. In the author's case the question might be raised concerning the role of adrenal cortical extract and DOCA in causing the glycosuria. DOCA does not have such a hyperglycemic effect and adrenal cortical extract has only a slight effect on the blood sugar even when given in large amounts.[11] Sugar was found in the urine after DOCA 1 mg. was given the day previously and ACE 10 cc. the day afterward. The relatively small amounts given would hardly seem likely to cause a persistent glycosuria over such a prolonged period.

In searching for an explanation of the hyperglycemia one thinks of the persistent hyperglycemia that is found as one manifestation of hyperactivity of the "S" hormone of the adrenal cortex as in Cushing's syndrome; of hyperactivity of the anterior lobe of the pituitary with overproduction of ACTH and possibly other hormones; or possibly hyperfunction of the alpha cells of the pancreatic islets which are thought to produce a hyperglycemia. No evidence of adrenal, pituitary or thyroid disease was noted. The glycosuria and metabolic changes could be due to toxic effects on a carbohydrate regulating mechanism in the brain as suggested by Strandqvist. It seems more likely due to a toxic effect on the islet cells of an immature pancreas.

## Summary

An example of a transient diabetic state in infancy is reported, together with a review of four others and a discussion of possible etiologic factors.

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SPANISH ABSTRACT

## Diabetes Transitoria en la Infancia

El autor describe un caso de diabetes transitoria en un niño de 13 días de edad, sin antecedentes diabéticos en la familia, que bruscamente presentó pérdida de peso, sin diarrea ó vómitos, fiebre de 101.8 F., y deshidratación intensa. Sospechándose insuficiencia suprarrenal se trató con desoxicorticosterona y extracto total de corteza suprarrenal. A las 24 horas se apreció glucosuria y a los 4 días se encontraron 555 mlgs. % de glucosa sanguínea en ayunas iniciándose entonces insulina, con la cual hubo una mejoría dramática del estado general ganando peso de allí en adelante, en forma progresiva. La fiebre fué contínua por los primeros 6 días, cedió por 48 horas y continuó por 7 días más con elevaciones diarias. Solo una faringitis ligera era su explicación posible y se trató por un mes con penicilina. Se apreció hepatomegalia a los 7 días de iniciado el cuadro y persistió por 2 semanas.

A los 54 días de iniciado el padecimiento la orina no presentaba glucosa y se suspendió la insulina, aproximadamente cuando tenía 2 meses de edad. A los 5 meses estaba sano y su desarrollo era normal para su edad.

Existen 57 casos reportados en la literatura, de diabetes en niños de menos de un año; entre ellos hubo 3 casos de cuadros diabéticos transitorios seguidos de mejoría y curación completa aparentemente. Dos de ellos estaban asociados con infección severa que aparentemente precipitó el proceso diabético y al curar las enfermedades coexistentes, desapareció la diabetes. El tercer caso estuvo asociado con una infección respiratoria superior pero pudo haber tenido ya los síntomas antes de la infección.

Es posible que la glucosuria y los cambios metabólicos sean el resultado de una acción tóxica sobre el mecanismo regulador cerebral del metabolismo de los hidratos de carbono aunque es mas probable que dicha acción se haga sobre los islotes de un pancreas inmaduro. Aunque estos 4 casos llenan la definición de la diabetes mellitus parece que debe haber alguna variación desconocida que los lleva aparentemente hacia la curación permanente.

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# EPIDEMIC SHIGELLA GASTROENTERITIS (BACILLARY DYSENTERY) IN AN ENDEMIC AREA

## II. Age-Specific Clinical Aspects

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HARDY and Watt,[1,2] in their studies of diarrheal diseases during the past decade, have expressed clearly what has now become the prevalent clinical picture of bacillary dysentery, and explained the alterations in both the variety and severity of the prevailing symptoms. The clinical course of the disease may be correlated with many factors—with the type of the Shigella organism which may be involved, with the success or failure of efforts to isolate the organism from the patient's stools, with the immune status of the individual, and with the age of the patient. Consideration of the first factor indicates that there seems to be no relationship between the clinical picture of the disease in the individual patient and the type of Shigella etiologically concerned.[1,3,4] In studying the second factor (isolation of organism), Hardy and Watt[1] compared 473 culturally positive with 692 culturally negative cases and could find no prominent differences in the associated symptoms and findings. An attempt to find some significant variations in symptomatology of the culturally positive and negative cases in the data to be presented in this paper also yielded similar results. The present relative mildness of acute bacillary dysentery has been explained by some investigators[3,5,6] by assuming a high degree of immunity to exist among native populations in areas endemic for a given type. The fourth factor which may operate closely with that just expressed (immunity status) is the age of the patient. It is the purpose of this presentation to study the relationship of age to the clinical pattern of the disease.

Bacillary dysentery is particularly serious at both extremes of life in terms of case-fatality rates. There are, however, many other indices of general severity such as the mode of onset, the totality of the symptomatology and the severity of each, the duration, recurrences, disability, sequelae and complications. The clinical pattern of bacillary dysentery among various age-groups as it appeared in an outbreak among the general population in an area in which it had always been highly endemic will be considered in this paper. Because of the distributional skewness of the age-group curve towards the younger age-groups, and the smaller number of individuals in the older age-groups, comparisons are to be considered suggestive rather than significant, and of particular interest to pediatricians.

An outbreak of acute bacillary dysentery occurred in 1949 on the Menominee Indian Reservation in Wisconsin. The disease is highly endemic in this region. Approximately 350 persons became ill, 169 cases were investigated and 162 studied. Epidemiologic diagnosis was based on a random sample of 31 clinically ill patients (about 20% of the group studied) from whom 33 stools were cultured. S. paradysenteriae (Flexner), not typed, was found in 14 cases. In four cases Pr. morganii was isolated and in one

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case Pr. rettgeri. These organisms were isolated from 10 to as much as 116 days after the onset of illness, averaging about 25 days from onset. A good deal of the difficulty encountered in the isolation of the Shigellae is due to the fact that, while they may persist for weeks or months in water and even on contaminated clothing, they disappear rapidly from the excreta of patients. During the first five days of illness positive cultures may be obtained in slightly over 60% of the stools of untreated patients, but after this time the percentage decreases rapidly despite the typical (pus and blood) nature of the stools.[7,8] Despite the long period between the onset of illness and time of collection of the fecal specimens, the percentage of positive cultures in this investigation was excellent and beyond expectation (58%). In view of the high percentage of negative cultures always obtained in outbreaks of this type, it has long been regarded as sound epidemiologic and clinical practice to consider all clinically similar cases as cases of bacillary dysentery. Some epidemiologic aspects of this outbreak along with a detailed description of the method of investigation have been published in a previous report.[6]

## Onset of Illness

Of 106 cases, 89 (or 84.0%) reached the height of their illness within 24 hours, 13 (12.3%) took 1 to 2 days, and in only four cases did the illness take three days to reach its maximum intensity (table 1). Abruptness of onset and rapid development of symtom-

TABLE 1

Rapidity of Onset of Illness in 106 Cases

| Height of Illness Reached in | No. of Cases | Per Cent of All Cases |
|---|---|---|
| 1 day | 89 | 84.0 |
| 2 days | 13 | 12.3 |
| 3 days | 4 | 3.8 |
| Total | 106 | 100.1 |

atology may be said to characterize this outbreak. This conforms closely with Hardy and Watt's[1] description in their study, 80% of culturally positive and 74% of the negative cases occurring within 24 hours. Such abruptness is also considered characteristic of typical sporadic cases, although the height of illness in this form is usually reached in 3 to 5 days.

## Symptomatology

The classical clinical picture of bacillary dysentery is a rarity today, particularly in this country. This is exemplified by table 2, which presents the general frequency of symptoms and their distribution at various age-group levels in 97 patients. While there is no outstanding pathognomic differentiation among the patients in the three age groups, some distinctions are worth noting.

The diagnostic triad of diarrhea, tenesmus and fever described by Felsen[3] is not apparent. Diarrhea, present in all cases, is far from a "bloody flux." The median (and average) number of evacuations per day for all age groups was 9 to 10, with a minimum of 3 and a maximum of 30. The interquartile range was 5 to 10 bowel movements per day. The presence of blood was not noted in even half the cases in any age-group. In the

TABLE 2

GENERAL FREQUENCY OF SYMPTOMATOLOGY AT VARIOUS AGE-GROUP LEVELS IN 95 CASES

| Symptom | Frequency in Per Cent | | |
|---|---|---|---|
| | 0–5 yr. (43 Cases) | 6–15 yr. (20 Cases) | 16 yr. and over (32 Cases) |
| Diarrhea | 100.0 | 100.0 | 100.0 |
| Blood | 28.0 | 40.0 | 9.4 |
| Abdominal Cramps | 62.8 | 60.0 | 81.3 |
| Fever | 62.8 | 55.0 | 34.4 |
| Anorexia | 53.5 | 60.0 | 50.0 |
| Vomiting | 44.2 | 35.0 | 28.1 |
| Headache | 34.9 | 70.0 | 62.5 |
| Weakness | 41.9 | 65.0 | 62.5 |
| Nausea | 34.9 | 35.0 | 34.4 |

0-5 year age-group (43 cases) blood in stools was noted in slightly over one quarter of the cases, and increased to 40% in the 6 to 15 year age-group (20 cases). In patients 16 years and over, blood was noticed in less than 10% of the cases. There was no significant or appreciable variation in the number of bowel evacuations per day between those (or a household member) in whom organisms were found by fecal culture, and those in whom no organisms were isolated. Nor was there any significant variation among these groups in respect to the other symptomatology. This is similar to the findings of Hardy and Watt[1] in their studies of diarrheal diseases. Tenesmus was observed in 60 to 80% of all cases, with no remarkable age-group distinction. Fever is not a necessary accompaniment of bacillary dysentery. It is more frequent in the youngest age-group (63% of cases) and decreases with age in the oldest age-group—from almost two-thirds the cases in the 0-5 year patients to about one-third in patients 16 years of age and over.

Anorexia was present in about half the cases in all groups. Nausea and vomiting were noted in about one-third the patients with vomiting occurring somewhat more frequently (44%) in the youngest age-group and decreasing with increasing age to 28% in the oldest group. Headache is present to a lesser degree among children under 6, and occurs twice as frequently in the older groups.

## DURATION OF ILLNESS

Duration of illness is difficult to estimate; each investigator establishes his own criteria and in many instances fails to state them. In general it is agreed that acute bacillary dysentery is a self-limited disease, with a termination of the acute symptomatology in about 10 days. If we accept Felsen's[3] concept that every infected (though asymptomatic) person is a sick person, then estimates of duration will be prolonged. Arbona and Gonzales[5] estimate the average duration of infection (not necessarily synonymous with duration of illness) at approximately 1 to 4 weeks. For clinical purposes, we are adhering to Hardy and Watt's[1] definition of duration as referring to the termination of the acute phase, the time when stools tend to become normal, strength is regained, and other complaints disappear. While not subject to exact measurement, in general the end of the acute phase is marked by a termination of the diarrhea.

TABLE 3

DURATION OF ACUTE ILLNESS IN 100 CASES

| Days | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16–20 | 21–30 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of Cases | 1 | 15 | 11 | 12 | 11 | 11 | 2 | 6 | 4 | 3 | 4 | 2 | 5 | 2 | 1 | 6 | 4 | 100 |
| Cum. Per cent | 1 | 16 | 27 | 39 | 50 | 61 | 63 | 69 | 73 | 76 | 80 | 82 | 87 | 89 | 90 | 96 | 100 | — |

$Q_1 = 2.8$ days $Q_2 = 5.5$ days $Q_3 = 9.7$ days

NOTE: There is no correlation between age of patient and duration of illness.

As measured by the cessation of diarrhea, the duration of acute illness was noted in 100 cases, and is presented in table 3. The median duration was 5.5 days, the interquartile range between 2.8 and 9.7 days. An effort was made to correlate the age of the patient with the duration of illness. No such correlation was found in this outbreak (footnote, table 3), although somewhat longer periods of illness among children than adults have been reported.[9] While in one study Hardy and Watt,[1] because of the wide variation observed, conclude that there is no usual duration, nevertheless, in a somewhat previous study,[2] referring to explosive outbreaks of Shigella infection they note a usual duration of 2 to 5 days.

## RECURRENCES

Of 162 cases 21 (13.0%) suffered recurrences (table 4). Of these, 5 were under 12 months of age, almost 36% of all the cases (14) in this age-group. There were 11 recurrences, representing 28% of 39 cases, in the age-group 12 through 23 months. Thus, of the 21 cases which recurred, 16 (76.2%) were in patients under 2 years of age.

Only one recurrence was noted in the 2 to 4 year group, and none in any of the groups through age 25. Three recurrences were reported in the 26 years and over age-group, representing almost 9% of all cases in this group.

Whether these recurrences were exacerbations of the original infection, or clinical manifestations of reinfection with the same or different types of Shigella could not be ascertained in this investigation. There are no criteria which clearly define what may or may not be considered a recurrence. A reappearance of acute symptomatology after a variable period of time is the most commonly recognized factor. We have accepted as recurrences those cases in which there was a return of the acute symptomatology after the apparent clinical recovery of the patient from his previous attack. It is appreciated that symptomatic freedom almost invariably precedes tissue restoration to normalcy (as determined by sigmoidoscopy), and may precede bacteriologic cure (which may be interpreted as freedom from the carrier state rather than as an absolute criterion of clinical recovery). The time interval between recurrent attacks varied from 4 to 122 days (table 4). Only one patient suffered a recurrence in 4 days (Case No. 122), and a second recurrence in 10 days. Should this case be disregarded, and considered as one of single relapsing illness, none of the essential data would be altered materially. The same applies to Case 99, a 4 year old child with a recurrence 8 days after his recovery, and 4 days after the recovery of a second case within the same household. Of the other

TABLE 4

AGE DISTRIBUTION OF RECURRENCES AMONG 21 CASES AND RELATIONSHIP TO INITIAL RECOVERY AND PRIOR HOUSEHOLD CASES

| Age Group | No. of Cases with Recurrence | Per Cent of Total Recurrences | Per Cent of All Cases in Age Group | Case No. | Age | No. of Recurrences | Days After Stated Recovery | Relation of Recurrence to Onset or Recovery of Prior Household Case | Comment |
|---|---|---|---|---|---|---|---|---|---|
| 0–11 mo. | 5 | 23.8 | 35.7 | 14 | 9 wk. | 2 | 51, 64 | No previous H.H. case | Died |
| | | | | 15 | 6 mo. | 2 | 37+ | Prior case still ill | |
| | | | | 46 | 10 mo. | 1 | ? | No previous H.H. case | Died |
| | | | | 67 | 7 mo. | 1 | 14 | No previous H.H. case | |
| | | | | 86 | 5 mo. | 1 | 14 | No previous H.H. case | |
| 12–23 mo. | 11 | 52.4 | 28.2 | 23 | 15 mo. | 1 | 69 | 50 days after onset | |
| | | | | 31 | 1 yr. | 1 | ? | | |
| | | | | 37 | 18 mo. | 1 | abt. 31 | No previous H.H. case | |
| | | | | 44 | 17 mo. | 1 | 35 | 8 days after recovery | |
| | | | | 47 | 15 mo. | 1 | 121 | 119 days after recovery | |
| | | | | 48 | 15 mo. | 1 | 122 | 3 days after onset | |
| | | | | 50 | 23 mo. | Often | ? | | |
| | | | | 55 | 1 yr. | Often | ? | | |
| | | | | 64 | 15 mo. | 1 | 23 | No previous H.H. case | |
| | | | | 102 | 1 yr. | Continuous | ? | | |
| | | | | 132 | 20 mo. | 1 | ? | No previous H.H. case | |
| 2– 5 yr. | 1 | 4.8 | — | 99 | 4 yr. | 1 | 8 | 4 days after recovery | |
| 6–10 yr. | 0 | — | — | | | | | | |
| 11–15 yr. | 0 | — | — | | | | | | |
| 16–25 yr. | 0 | — | — | | | | | | |
| Over 25 yr. | 3 | 14.3 | 8.8 | 24 | 26 yr. | 1 | ? | 18 days after recovery | |
| | | | | 26 | 49 yr. | 1 | 47 | No previous H.H. case | |
| | | | | 122 | 32 yr. | 2 | 4, 10 | No previous H.H. case | |
| Unknown | 1 | 4.8 | — | 30 | ? | 1 | ? | | |
| Total | 21 | 100.1 | 13.0 | | | | | | |

Total recurrences among cases under 2 yr. of age=16 or 76.2% of all recurrences and 30.2% of all cases (53) in this age group.

cases in which information was obtainable, 2 recurred 14 days after clinical recovery (Cases 67 and 86); one, 23 days after recovery (Case 64), and all the others after one month. Ten of the cases which recurred were in households in which there were no other reported cases; in 7 instances other cases had also occurred in the same household during the period intervening between attacks; but at markedly varying intervals.

## Fatality Rates

Two deaths were recorded among the 162 cases (table 5). Both were under one year of age. The case-fatality rate for this age-group is 14.3%. This is a relatively low rate, but as noted in Appendage A of table 5, there were five other diarrheal deaths in the area which were not included in the tabulation. Three of the deaths were in infants

TABLE 5

Case-Fatality Rates

| Deaths | Ages | No. of Cases in Age Group | Case Fatality Rate |
|---|---|---|---|
| 2 | 9 wk.<br>10 mo. | 14<br>(under 1 yr.) | 14.3% |

A. Other Diarrheal Deaths in Area Not Included in This Study—Between Sept. 18 and Oct. 20

| | Age | Date of Death | |
|---|---|---|---|
| 1. | 5 mo. | 9/18/49 | Bronchopneumonia—chr. diarrhea |
| 2. | 7 mo. | 9/23/49 | Bronchopneumonia—chr. diarrhea |
| 3. | 2 wk. | 9/30/49* | Infant diarrhea |
| 4. | 2 wk. | 10/4/49 | Bronchopneumonia+chr. diarrhea |
| 5. | 2 wk. | 10/10/49 | Infant diarrhea |

* Father of this infant was a case of "chronic diarrhea." In this family of 10, another infant developed diarrhea in November.

2 weeks of age, one 5 months of age and one 7 months of age. In three of the cases bronchopneumonia was listed as the primary cause of death with chronic diarrhea as a contributing cause; "infant diarrhea" was listed as the primary cause in the other two cases. The listing of diarrhea as a contributing cause in infant deaths is far from uncommon, and must be taken into consideration to obtain a more accurate picture of the seriousness of bacillary dysentery among infants.

## Comment

The classical form of bacillary dysentery admits of ready clinical diagnosis, but the vastly more common and milder forms present obvious difficulties to clinical differentiation. Most cases which come to the attention of the physician will remain undiagnosed if he retains a clinical concept of acute bacillary dysentery as an entity comprising almost innumerable daily stool evacuations of bloody mucopurulent consistency, accompanied by abdominal pain and fever.[3] Even before the advent of antibiotic therapy, this almost pathognomonic triad ceased to exist. The absence of blood in the stools (or at most the presence of specks) is the usual finding. Moreover, afebrile bacillary dysentery can no longer be considered a paradoxic form of the disease; it occurs much too frequently.

Changes in host-parasite relationships are observed continuously, both on an individual and species basis. Such changes may be effected through alterations in the virulence

of the parasite or any of its varieties, and through changes in the susceptibility or resistance of the host. In many instances both factors are operative, and when so it is difficult to estimate the relative roles of each. Several guides are available for such evaluation. One such guide may be afforded by a study of the disease pattern which is produced among persons in areas where infection by a given organism, or one or more of its particular strains, predominates, as compared with the disease pattern which occurs in susceptible hosts not previously exposed to the organism or type under consideration (such as has been determined for syphilis, tuberculosis and rubeola, for example). Another guide may be found in sero-immunologic studies among general and selected population groups.

This paper presents the clinical pattern of bacillary dysentery in an area where any immunologic factors which may exist because of repeated previous exposures to Shigella must certainly be considered operative. A study of the age-specific disease pattern has been considered because the attack-rates are greatest in the first two years of life, and seem to rise markedly after the first six months.[10] Estimates of severity of an illness should be based upon more than age-specific case-fatality rates, and this paper represents an effort to do so. However, the relationship of the immunity factor (due to repeated previous exposures) with the milder clinical picture which may accompany it cannot be demonstrated by comparing the clinical picture as observed among a single age-group during one epidemic with that of a similar age-group in a second epidemic. In different outbreaks, different types of the Shigella genus may be implicated, and the variations in the previous exposures of the populations which are compared might well be so great that no valid comparisons concerning the immune status of the same or differing age-groups should be made. Such can only be accomplished by studying variations of the age-specific clinical picture as it occurs among an entire general population group epidemically involved by the disease in statistically significant numbers. When enough such studies have been made, it will be possible to fully evaluate the degree of immunity produced by the acknowledged endemicity of bacillary dysentery, particularly when compared with similar studies in nonendemic areas. The age-specific incidence and symptomatology for groups under two years may yield information concerning the transfer of immune bodies transplacentally in this disease. Additional material may be supplied by studying the disease picture which may occur among large population masses who may be required to shift from native homelands where one type of the Shigella genus has been predominant to lands where another type prevails.

For the purposes outlined above sero-immunologic studies alone are as yet far from satisfactory.[10] In using clinical patterns for such purposes, however, one need becomes very apparent. Investigators must define some of the basic terms they use in description. If no uniformity can be achieved, certainly each writer must be aware of his responsibility to state clearly just what he means when using these terms. Such lack is too common in the literature of bacillary dysentery, and the compilation and comparison of previously reported data becomes almost impossible and usually is statistically invalid.

## Summary

The clinical aspects of acute bacillary dysentery as observed in an outbreak among a general population group in a highly endemic area are presented; age-specific clinical variations are noted.

The onset was abrupt in all cases and all age-groups. The height of the illness in

84% of 106 cases was reached in 24 hours, more rapidly than in the "classical" form (3 to 5 days).

The presence of blood in the stools was noted in about 25% of all cases; in about 25% of the 0 through 5 year age-group, 50% of the 6 through 10 year group, 37½% of the 11 through 15 year age-group, and 9 to 10% in the groups 16 years of age and over.

The median number of stools was 9 to 10 daily, with no significant difference among the various age-groups.

Fever was present in 65% of the children 10 years of age and under (55 cases), and in 35% of the older age-groups (40 cases).

Vomiting is more frequent among the younger age-groups; weakness becomes a more frequent complaint with advancing age.

The median duration of illness was 5.5 days in 100 cases. There was no correlation observed between age and duration.

Recurrences are more frequently observed in the youngest age-groups—36% of all cases (14) under one year of age, 28% of 39 cases between 1-2 years of age. About 9% of the 26 and over age-group (34 cases) recurred, and practically none in the intervening groups.

No relationship was observed between the tendency towards recurrences in households with multiple cases as compared with single cases.

All the fatalities were under one year of age. Two deaths occurred in the cases studied, yielding an age-specific death rate of 14.3% for this group. Five other deaths in cases not included in this report are noted, all under one year of age; 2 caused by "infant diarrhea" and 3 by bronchopneumonia with "chronic diarrhea" as a contributing cause.

The role of acquired immunity in the modification of bacillary dysentery can be evaluated from studies of attack rates and the clinical course of the disease, through age-specific groupings. Investigators should clearly define such basic terms as duration, recurrences, etc., when reporting so that necessary comparisons and/or data summation can be made.

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SPANISH ABSTRACT

## Gastroenteritis Epidémica por Shigela (Disentería Bacilar) en una Area Endémica

### II. Aspectos Clínicos por Edades Específicas

El propósito de este trabajo es hacer un estudio del cuadro clínico de esta enfermedad en relación con la edad, en un grupo de 162 casos que cayeron enfermos durante una epidemia de disentería bacilar aguda ocurrida en el estado de Wisconsin durante el año de 1949 en una zona en que la enfermedad es altamente endémica y que afectó a 350 individuos en total.

Existen algunos estudios que tratan de describir el cuadro clínico de la disentería bacilar que prevalece actualmente y de explicar las alteraciones en la variedad y severidad de los síntomas predominantes.

La evolución clínica puede correlacionarse con diferentes factores, como el tipo de shigela que produce el cuadro que parece que no hay relación alguna evidente; con el fracaso o éxito para aislar el bacilo de las evacuaciones tampoco encontrandose diferencia prominente entre los cuadros clínicos del grupo con coprocultivo positivo y con coprocultivo negativo; con el estado de inmunidad del individuo que ha sido aceptado como responsable de la relativa benignidad actual de la disentería bacilar por algunos investigadores, asumiendo que existe un alto grado de inmunidad entre las población nativa de las áreas endémicas para un tipo dado de shigela y finalmente, con otro factor que podría actuar íntimamente con el estado de inmunidad y es el que se refiere a la edad del enfermo. Este aspecto es el que el autor estudia y reporta sus conclusiones en la presente comunicación, no limitándose a evaluar la severidad del padecimiento desde el punto de vista de los índices de mortalidad, mas altos en los extremos de la vida, sino también otros aspectos que pueden indicar la intensidad general del padecimiento como la forma de principio, la totalidad de la sintomatología y la severidad y duración de cada síntoma, recaídas, incapacidad, secuelas y complicaciones.

Las conclusiones del autor las resume así:

1. El principio fué súbito en todos los casos y en los grupos de todas edades. El acmé de la enfermedad se alcanzó a las 24 horas en el 84% de 106 casos investigados, siendo más rápido que en la forma "clásica" (3 a 5 días).
2. La presencia de sangre en las evacuaciones se apreció en mas o menos el 25% de todos los casos y estudiado por edades se encontró en el 25% del grupo 0 a 5 años, en el 50% en el grupo de 6 a 10 años, en el 37.5% en el de 11 a 15 años y de 9 a 10% en los grupos de 16 años para arriba.
3. El número promedio de evacuaciones fué de 9 a 10 diariamente, sin diferencias de significación entre los distintos grupos de edades.
4. Hubo fiebre en el 65% de los niños hasta los 10 años de edad inclusive (55 casos) y en el 35% de los enfermos de los grupos de mayores edades (40 casos).
5. El vómito es mas frecuente entre los grupos de edad mas corta y la debilidad se hizo mas común a medida que avanzaba la edad.
6. La duración media de la enfermedad fué de 5.5 días en 100 casos. No hubo correlación entre la edad y duración del padecimiento.
7. Las recaídas se observaron mas frecuentemente en los grupos de edades mas bajas: 36%, de todos los casos (14) por abajo de un año de edad, 28% de 39 casos que formaban el grupo de 1 a 2 años de edad, 9% de 34 casos que cayeron en los grupos por arriba de los 25 años de edad, y practicamente ninguna entre los grupos intermedios. No se observó relación entre la tendencia a las recaídas en casos con múltiples pacientes en comparación con los casos únicos.
8. Todas las muertes ocurridas se registraron por abajo del año de edad. Dos fallecimientos hubo en los casos estudiados, dando un coeficiente específico por edades de 14.3% para este grupo. Hubo otras 5 muertes en casos no incluídos en este reporte, todas abajo de un año de edad, dos causadas por "diarrea infantil" y tres por bronconeumonía, con "diarrea crónica" como causa contribuyente.
9. El papel de la inmunidad adquirida en la modificación de la distentería bacilar puede ser evaluado por medio del estudio de los coeficientes de ataque y de la evolución clínica de la enfermedad a traves de grupos específicos de edad. Los investigadores deben definir claramente tales terminos básicos como duración, recaídas, etc, cuando los reporten, de manera que puedan hacerse, si se hace necesario, las comparaciones y suma de datos o exclusivamente esta último.

*1 West Wilson Street*

Pediatrics

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# AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

## SUMMARY OF THE ANNUAL BUSINESS MEETING

The Annual Business Meeting of the American Academy of Pediatrics was held at the Palmer House, Chicago, at 2:10 p.m., Wednesday, Oct. 22, 1952. Dr. Warren W. Quillian, President of the Academy, presided.

It was moved, seconded and carried that the reading of the minutes of the last meeting be dispensed with and that they be approved as published.

Dr. Lee Forrest Hill was appointed to serve as parliamentarian of the meeting.

President Quillian paid tribute to the industry and efforts of the Board, and mentioned the following highlights from the abstracted report of the meeting:

A tentative plan for life membership, as proposed by the Committee on Life Membership, was approved by the Board and definite plans will be available to the membership after the semi-annual meeting of the Board in 1953, so that those members 50 years of age and over, who wish to avail themselves of life membership classification, will have that privilege.

The Board is thoroughly aware of the inadequacy of pediatric training in internship and discussed this question at length, and went on record as approving the Medical Education Committee's efforts toward making improvements.

The report of the Executive Secretary was read by the Executive Secretary, Dr. E. H. Christopherson, as follows:

"The American Academy of Pediatrics has just concluded a successful year when judged by standards of business operation; increase in membership; the activity of the officers, state chapters, Academy committees and Liaison Representatives; the success of the meetings and of PEDIATRICS and our relationships with other organizations.

"In May of 1952, 150 new Fellows were accepted into the Academy. At this October meeting 209 applications will be considered, so that we can safely say that approximately 359 new members will have been taken into the Academy this year. That will give a total active membership of about 3260 Fellows and including Emeritus, Honorary and Associate Fellows, the entire membership will be approximately 3439. The Academy continues to grow at a rate of about 10% per year.

"The various Districts of the Academy had the following distribution of Fellows as of September 1952:

| | | | | | |
|---|---|---|---|---|---|
| District | I | 252 | District | VI | 314 |
| District | II | 474 | District | VII | 343 |
| District | III | 286 | District | VIII | 404 |
| District | IV | 305 | District | IX | 310 |
| District | V | 363 | | | |

"There are organized chapters of the Academy in 21 states. Pennsylvania has effected its chapter organization, as has South Carolina. Tennessee and the Northern Section of California have indicated that they intend to organize chapters.

"It is rather obvious to the Central Office that the Academy is much more effective in promoting

its objectives in those states where there are organized chapters. Having a state chapter does not mean that it is necessary to hold more meetings or to make more noise about the Academy, but it does seem that a state chapter as the representative of a national organization is able to carry much more weight when it is necessary to deal with medical societies, hospital staffs, health departments and other organizations.

"The officers of the Academy have devoted much more time to the affairs of the Academy. The President and President-elect have represented the Academy at many meetings and special functions, as have some of the District Chairmen.

"The Treasurer has visited the Central Office on 2 occasions to review the financial situation of the Academy and to counsel with the Executive Secretary.

"All the officers have been most helpful in assisting the Executive Secretary.

"The business affairs of the Academy are in good order. During the past fiscal year the Central Office operated within the prescribed budget with some saving to the Academy. All of the budgeted committees have likewise stayed within their appropriations. The budget for the 1952-53 fiscal year is a little less than the budget for the 1951-52 year which has been made possible by the adoption of several stream-lining procedures and by the acquisition of labor- and time-saving equipment. The move to the new office location saves in rent. The purchase of an off-set printing machine makes it possible to do about 90% of the required printing in the office, with special paper purchases, another saving.

"News-Letters have been increased from 4 last year to 10 this year.

"The increased committee activities, plus more News-Letters and more information regarding meetings has resulted in a great increase in mail, both coming into and going out of this office. In July and August of this year 15,500 pieces of mail were sent out from the office. In a 12 months' period this would mean 93,000 items and an average of 348 pieces a working day.

"During the year the Executive Secretary has met with members of the Academy in Washington, Boston, Miami, Chicago, St. Louis, San Francisco, Los Angeles, Buenos Aires, Rio de Janeiro and Mexico City. The Third Pan American Congress of Pediatrics was attended in Montevideo.

"Meetings with 9 of the Academy's Committees have been held. Frequent get-togethers with both the Editor and the publisher of PEDIATRICS have been arranged.

"The meetings of 6 other medical organizations have been attended.

"Conferences have been held with representatives of 27 societies interested in child welfare.

"The Academy has worked cooperatively on programs with the American Medical Association, the American Public Health Association, the National Safety Council, the National Health Council, the P.T.A., the National Education Association, the New York State Department of Health, the Research Foundation, American Hospital Association, The National Conference on Citizenship, the National Foundation for Infantile Paralysis, the National Society for Crippled Children and Adults, the American Standards Association and the Metropolitan Life Insurance Co.

"It will be seen after reading the various committee reports that the majority of the Academy's 29 committees have been very active during the year. These committees devote much time and effort to the study of problems and in preparing reports and recommendations that are of incalculable value to the members of the Academy and often to the entire medical profession of the Americas, and of course, ultimately add to the progress being made in Child Health.

"A new revised edition of the Report of the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases (the Red Book) has been published. Several other reports and recommendations are being prepared. The Red Book and the *Standards and Recommendations for Hospital Care of the Newborn* are used extensively by schools, health departments and hospitals. The Committee on Accident Prevention prepared the pamphlets *Are You Using the New Safety Vaccine?* and *A Formula for Child Safety* in cooperation with the Metropolitan Life Insurance Company. The Committee on Medical Education published, as a supplement to PEDIATRICS, the *Report on Regional Conferences of Pediatric Educators.*

"PEDIATRICS, the official journal of the Academy, continues to prosper. The distribution is now around 7100 and the journal is doing very satisfactorily from a financial standpoint. PEDIATRICS is considered as a superior journal and we should be most appreciative of the efforts of the Editor and the Editorial Board.

"The 25 Liaison Representatives of the Academy to organizations working all or in part in areas of child welfare have kept the Academy informed as to the activities of these organizations. They

have also served in the capacity of advisors to the other groups and in many instances have brought about very worth while co-operative programs.

"As might be expected with the growth of the Academy, both the Annual Meetings and the Areal Meetings are increasing in size. The 2 meetings this year have been successful ones from the standpoint of good programs, attendance and financial remuneration.

"Every effort is being made and will continue to be made to make the meetings more interesting and attractive to the members. The members are now given a great advantage in the fees paid and only members may register for Seminars, Round Tables and procure banquet tickets in advance of the meeting. The headquarters hotel also gives preference to members. The size of our meetings will in the future more and more limit the sites where meetings can be held.

"Before closing it should be mentioned that the Business Manager and the entire Central Office staff have worked hard and diligently and are all contributing much to the success and welfare of the Academy. The Executive Secretary appreciates their interest, diligence and loyalty very much."

It was moved, seconded and carried, that the report of the Executive Secretary be accepted.

The Executive Secretary then announced the results of the election of district chairmen and alternate district chairmen as follows:

District I—Alternate District Chairman, Dr. Robert M. Lord, Providence, R.I.

District III—District Chairman, Dr. Joseph A. Gilmartin, Pittsburgh.

District IV—Alternate District Chairman, Dr. William Weston, Jr., Columbia, S.C.

District VII—Alternate District Chairman, Dr. Oliver W. Hill, Jr., Knoxville, Tenn.

The Executive Secretary then called attention to the names of the new fellows as listed in the printed agenda. There were 209 new members distributed by Districts as follows:

| | | | |
|---|---|---|---|
| District | I | 16 new members | 1 Affiliate in Surgery |
| District | II | 22 new members | |
| District | III | 13 new members | 2 Affiliates in Surgery |
| District | IV | 20 new members | |
| District | V | 29 new members | |
| District | VI | 19 new members | 1 Affiliate in Surgery |
| District | VII | 26 new members | 1 Affiliate in Surgery |
| District | VIII | 27 new members | |
| District | IX | 32 new members | |

The names of the 18 members who were elected to Emeritus Fellowship were read. (These names are listed in the abstract of the Executive Board meeting.)

Two members were granted an extension of leave of absence for one year: Dr. Gerti Dooneief, New York, and Dr. Amelia Sheftall Geeslin, Jacksonville, Fla.

Leaves of absence of one year were granted to 4 fellows.

The Executive Secretary had been notified of the death of the following 11 members since the last meeting:

Dr. Elmer Walter Barron, Rockland, Mass. (Emeritus)
Dr. Malvin Finkelstein, Jersey City, N.J.
Dr. Norman L. Hawkins, Watertown, N.Y. (Emeritus)
Dr. Rockwell M. Kempton, Saginaw, Mich.
Dr. Louis Charles Rosenberg, Newark, N.J.
Dr. Oscar M. Schloss, Southold, Long Island, N.Y.
Dr. Eugene H. Smith, Ogden, Utah.
Dr. LeRoy T. Stokes, Haverhill, Mass.
Dr. James J. York, Schenectady, N.Y.
Dr. Jaime Ramirez Acha, LaPaz, Bolivia.
Dr. Joseph S. Wall, Washington, D.C. (Emeritus)

*President Quillian:* "Clifford Grulee, very appropriately, as our Honorary President and as a long-time associate and friend of Dr. Joseph Wall, one of our deceased members, who was a Past President of this organization, will address a few remarks to the members, as a tribute to Dr. Wall."

*Dr. Clifford Grulee:* "I need not tell you that this is a very sad occasion for me, because nobody was closer to me than was Joe Wall.

"Dr. Joseph Stiles Wall was born in Washington, D.C., on Oct. 3, 1876. He received his early education in that city, graduating from the Central High School in 1893. He then attended the School of Medicine, Georgetown University, where he graduated in 1897. He took his graduate training at the Garfield Memorial Hospital and Children's Hospital and later the Providence Hospital. After postgraduate work in New York and Oxford, England, he began the practice of medicine in Washington.

"On May 29, 1909 he married Agnes Reimer of Brooklyn, N.Y. They had only one child, Frances, who is still alive.

"Dr. Wall held various teaching positions in Georgetown Medical College but his chief interest always lay in pediatrics and he became Assistant Professor of Diseases of Children of Georgetown University in 1897. From then on, he progressed rapidly, teaching in the departments of chemistry, pathology, physiology, as well as pediatrics, and was named Professor of Clinical Pediatrics in 1912. This position he held for many years until he resigned from his active work in 1951.

"Dr. Wall received many honors. He was twice honored by the Medical Society of the District of Columbia—being given a citation on Dec. 6, 1929, and later serving as its president.

"The American Academy of Pediatrics elected him to the presidency in 1944 and during his period of service he was granted an illuminated scroll for his activities in behalf of that organization.

"In July 1947 the President of Cuba presented him with the Decoration of Merit Order of Carlos I. Finlay.

"During his long and active medical life, Dr. Wall contributed to medical literature and was especially active in meetings. He was an excellent speaker, having a very great command of English, and therefore, was in much demand for his services both in medical societies and in social affairs. For many years he was the spokesman for the Academy at Congress and carried on most efficiently in that capacity. Later, as President of the Academy, he presented most forcibly the prevailing attitude of the members as against the Pepper Bill.

"Few who knew Dr. Wall but loved him. The proof of a kindly nature and loved by all is the patriarchal position which he held in Washington, D.C. It is from one's neighbors that one learns the truth of individual values and certainly no one was held in higher esteem than was Joseph Wall. Those of us who have seen him in meeting and in council feel that deep regret which is without expression. One wonders how a man so big could have been so humble. This Academy has not only lost a friend and an ex-President, but it has lost a counselor whose place cannot easily be filled.

"I should like to ask that this be put on the minutes and a copy sent to his daughter."

*President Quillian:* "That will be done, if it meets with the approval of the members, and in token of respect to our departed ex-President, I will ask the members to stand with bowed heads."

(The members rose and stood for one minute in silent tribute to the memory of Dr. Joseph Wall.)

The report of the Treasurer was then presented by Dr. Edgar E. Martmer, Treasurer of the Academy:

"The fiscal year of July 1, 1951 to June 30, 1952 closed in a very satisfactory manner. As of July 1, 1951 the cash balance on hand amounted to $133,089.42. This sum included restricted grants, special reserves and Central Office operating funds. The total cash receipts amounted to $297,342.88 of which $78,219.48 was received as dues.

"Cash disbursements amounted to $295,607.32, resulting in an increase of Cash Reserves of $1,815.56.

"Your attention is drawn to the fact that dues received from members amount to only 91.4% of the ordinary recurring expenses of operating the Academy.

"The Budget Control System has operated in a very satisfactory manner. It is a pleasure to report that all activities have been carried on within the limitations of the various budgets. Improvements have been made in accounting practices in the Central Office, and your Treasurer takes this opportunity to thank Dr. Christopherson, Mr. W. J. Becker, Business Manager, and Mr. E. J. Wiedman, auditor, for their fine cooperation.

"A detailed statement of cash receipts and disbursements will be published in PEDIATRICS."

It was moved, seconded and passed that the Treasurer's report be accepted.

*President Quillian:* "Under the classification of New Business, we wish to take action on the

proposed changes in the Constitution and By-laws. I will ask Dr. Stewart Clifford, as Chairman of the Committee, who is thoroughly familiar with this phase of the work, if he will make such comment as seems pertinent."

Dr. Clifford summarized the proposed changes with the members following step by step on the printed copies handed to each member at the meeting.

At the request of Dr. Paul Beaven, Dr. Clifford defined "Associate Member": "Those persons who, because of valuable service in any of the fields allied to pediatrics, are qualified to render assistance to the Academy in the accomplishment of its purposes, may be elected to Associate Fellowship." This type of membership has been reserved for extremely outstanding individuals. "It is considered a very honorary recognition to a man or a woman who has accomplished outstanding feats in any field allied to pediatrics. I think Dr. Hiscock was the last Associate Member elected."

It was moved, seconded and carried that the proposed changes in the Constitution and By-laws be accepted in toto, since the information had been provided for circulation earlier.

*President Quillian:* "Many of you are aware of the fact that the next annual meeting will be held in Miami, in the early part of October, and that following this occasion the International Congress of Pediatrics will be held in Havana at the University of Havana School of Medicine, from Oct. 12 to 17. We have with us today Dr. Felix Hurtado, who wishes to address a few remarks to the assembly on this subject."

Dr. Hurtado extended an invitation from the Cuban Organizing Committee to the fellows of the Academy to attend the Seventh International Pediatric Congress to be held Oct. 12 to 17, 1953.

Several resolutions were then read by the Executive Secretary, as follows:

I.

*"Be It Resolved,* That the American Academy of Pediatrics expresses its sincere appreciation to Drs. George F. Munns and John R. Vonachen, Chairman and Co-Chairman of the Local Committee, and members of the Chicago area, for their splendid cooperation in the planning and conduct at the Annual Meeting held at the Palmer House, Oct. 18 to 23, 1952.

II.

*"Be It Resolved,* That the American Academy of Pediatrics expresses its sincere appreciation to Drs. Tom Mitchell, T. H. G. Drake and Alfred E. Fischer for their untiring efforts in arranging the scientific exhibits of this meeting.

III.

*"Be It Resolved,* That the American Academy of Pediatrics expresses its appreciation to the management of the Palmer House for the cooperation of executives as well as employees during the period of the Annual Meeting held Oct. 18 to 23, 1952.

IV.

*"Be It Resolved,* That the American Academy of Pediatrics expresses its sincere appreciation to the Chicago Convention Bureau, Inc., and especially to Mr. Chester A. Wilkins, Executive Director, and his assistant, Miss Marlene Roberts, for their assistance during the meeting.

V.

*"Be It Resolved,* That the American Academy of Pediatrics expresses its sincere appreciation to the Ladies' Committee, Mrs. Harry L. Faulkner and Mrs. James B. Gillespie, and the wives of the Chicago members and pediatricians for their fine cooperation.

VI.

*"Be It Resolved,* That the American Academy of Pediatrics sincerely appreciates the courtesy of the Borden Company; Carnation Company; Libby, McNeill & Libby; Mead Johnson & Company; Pet Milk Company; M & R Laboratories; in providing the special events for members and their wives attending this meeting."

The 6 resolutions above were adopted as read, on motion made, seconded and carried.

*Dr. William W. Jones (Colorado):* I ask the privilege, Mr. Chairman, of presenting a resolution:

"BE IT RESOLVED, That the Fellows of the American Academy of Pediatrics, in session at this Twenty-first Annual Meeting, do hereby express their sincere appreciation to the officers of the Academy, the Executive Board, Dr. Christopherson, the Executive Secretary, Mr. Becker and the staff, for the excellent manner in which all of the affairs of the Academy have been managed throughout the year and for their untiring efforts in our behalf."

On motion made, seconded and carried, the resolution was adopted.

*President Quillian:* "We turn now to the presentation of the Clifford G. Grulee Award, and it is very appropriate that Dr. Grulee himself make this presentation. Dr. Grulee."

*Dr. Clifford Grulee:* "I am deeply grateful to this society for honoring me with this award. I don't know that I deserve it, but I certainly appreciate it.

"At this time the award goes to a man who started out early to work in his state. He became State Chairman. He became District Chairman. He became President, and he hasn't quit yet. He is very active in committees now. There is no man who has done more for the Academy, that I know of, or who has done it more willingly or more efficiently, and it is a great pleasure for me to give this award to Dr. Lee Forrest Hill."

(The audience rose and applauded for some time, as Dr. Grulee presented the Clifford G. Grulee Award to Dr. Lee Forrest Hill.)

*Dr. Lee Forrest Hill:* "Dr. Grulee and Members, I am sure I share the feeling of those this morning who received their scientific awards, when I say that it is rather difficult to express one's feelings at a time like this. I appreciate tremendously that my colleagues have seen fit to bestow this award upon me, and one other facet to it that gives me a great sense of appreciation is to receive it from Dr. Grulee himself.

"I would like to say just a word to some of the younger men who are coming up. An Academy organization like this was not just developed out of thin air. It has taken work, and hard work. What I want to say is this, that while I have put in a lot of time, I have been more than repaid for any amount of time that I have put in or any financial sacrifice that I have made, by the friends I have made over the country. If I had it to do all over again, I would do it exactly the same way, and I hope those of you who are coming along will feel that it is a worth while type of work, and I am sure that the friends you make will be a great reward to you. Thanks very much."

President Quillian then read the Presidential Address, during which he made the following interpolation:

"Because Dr. Pease is such a self-effacing person, many of the younger people here do not know him personally. I would like at this time, as a token of our esteem, to have Dr. Pease stand and receive a round of applause." (Dr. Marshall C. Pease rose. Applause.)

Dr. E. H. Christopherson read the report of the Nominating Committee. The Committee had selected as its nominee for the office of Vice-President (President-Elect) Roger L. J. Kennedy, of Rochester, Minn.

The President asked if there were any nominations from the floor. There were none.

A motion was seconded and carried that the report of the Nominating Committee be accepted.

Dr. Kennedy was then called to the platform.

*Roger L. J. Kennedy:* "Mr. President and Fellows: Today, when one speaks of the American Academy of Pediatrics, one speaks of nearly 3500 individuals, united by the common bond of interest, promotion of health of children, and engaged in furthering that interest by their efforts as individuals by their joint contributions to the organized program of this society.

"In the membership of this society are leaders in every field of pediatrics—research, education, editing and publishing, and in the utilization of these with the improvement of clinical practice and public health procedures. The sum total of the knowledge and skills represented in this group is great. The disciplines are many and varied and the potentialities of accomplishment of purpose incalculable.

"When, therefore, the American Academy of Pediatrics pauses for a moment to confer on one of its members the highest honor within its power, the recipient cannot but compare his own slight stature to that of colossus. It is with such a feeling, mixed with those of wonder and gratitude, that I accept the honor and pledge to each and all of you my best efforts. May God continue to guide our deliberations and actions. Thank you."

(Dr. Paul Beaven and Dr. Crawford Bost escorted President-Elect Dr. Philip Barba, to the platform, where President Quillian pinned the President's badge on his coat and gave him the gavel.)

*President Barba:* "I still don't know how I was pushed up into this elevated position. I do not have the graceful, witty and talented ability of Warren Quillian to put things on an easy groove, and I am sure I don't have the astuteness and the firmness of Roger Kennedy. I assure you, however, that I will rely on both Warren Quillian and Roger Kennedy to help me in the performance of my duties, in addition to the very, very able Executive Board that we have working for us. I am sure you realize that this is a team play proposition, and that the President, while he has a lot of work to do and a lot of responsibility, has a great many helpers, not only among our Executive Board but, as was stressed earlier today, among all members of the Academy.

"I am not going to make any more of a speech than that, but since the 'blacksnake whip' has been transferred to my hand, I must announce that there will be an Executive Board meeting immediately after this in Room 9, on the third floor. Thank you very much. I am reminded that I am in charge and that a motion for adjournment is now in order."

Upon motion made and seconded, the meeting adjourned at 3:50 p.m.

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Leon Chrem, Colmena Derecha No. 223, Lima, Peru
Orlando Orlandini T., Av. Olavegoya 1821, Lima, Peru

*Round Table Discussion*

# NATURE, RECOGNITION AND MANAGEMENT OF NEUROMUSCULAR DISABILITIES IN CHILDREN

MEYER A. PERLSTEIN, M.D., Chicago, *Chairman;* EUGENE T. MCDONALD, ED.D.
State College, Pa.

*Chairman Perlstein:* In neuromuscular disabilities there are many problems to consider. However, about half of these comprise that group of diseases we know as cerebral palsy. We will start by orientating ourselves toward cerebral palsy, and in the discussion taking up the question of differential diagnosis and related subjects.

Cerebral palsy is not a single disease but a group of conditions which have in common a disorder of the motor system. It can be paralysis, incoordination, tremors or excessive motions, due to involvement of the motor centers of the brain. In other words, palsy and cerebral are defined. The important thing about cerebral is that the motor centers must be involved. If the problem is lack of development because of mental deficiency, you can exclude it. Likewise, spinal palsy, polio, and other causes of motor defects not due to involvement of the motor center are excluded. In schools for children with physical handicaps of all types, about half the children are cerebral palsied. So, from the viewpoint of frequency, cerebral palsy is the most frequent of the disabling conditions.

Much confusion exists in the terminology and classification of cerebral palsy. The term "Little's disease" has often been used as a generic term to cover all forms of cerebral palsy. Actually, Little described only one of the many types. Likewise, the term "spastic" is often used by the doctor and laymen to cover all categories. This tendency is conducive to loose thinking. A logical classification of the types of cerebral palsy would help to clarify this confused subject. Classification may be according to: (1) anatomic site of lesion; (2) the qualitative nature of the clinical symptom present; (3) the topographic involvement; (4) the degree of tonicity, (5) severity of involvement and (6) etiology. These naturally overlap.

## CLASSIFICATION ACCORDING TO ANATOMIC SITE

1. Pyramidal
   Clinically spastics
2. Extrapyramidal or basal nuclear
   Clinically athetoids, tremors or rigidities
3. Cerebellar
   Clinically ataxics

The pathologic classification is not too helpful since it presumes knowledge we do not have. Actually, cases in whom extrapyramidal rigidity has been diagnosed have been found to have cerebellar aplasia. Likewise, cases in which the clinical diagnosis was athetosis were found to have normal basal nuclei and only cortical changes.

## CLASSIFICATION OF CLINICAL EVALUATION

1. Spastic—"upper motor neuron lesion"—stretch reflex
2. Dyskinesias (motion and tone)
   (a) Chorea—involuntary, unpredictable, incontrollable with excess motion—little tone
   (b) Athetoid—same with more tension
   (c) Dystonia—same with marked tension
   (d) Tremor—pendular, agonist-antagonist
   (e) Rigidity—greatest resistance to slow motion
      (1) lead pipe
      (2) cogwheeling
3. Ataxia—dyssynergia, loss of balance sense

From the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 21 and 22, 1952.

The clinical classification is perhaps the most useful. The term spastic is used in the Sherrington sense of indicating a lesion of the pyramidal tract. There is an increase in the stretch reflex. This is an exaggeration of the physiologic property of normal muscles to contract when they are passively stretched. It is elicited by a rapid stretch of the muscle and eliminated by a slow stretch. It is more common in the antigravity muscles. This is to be differentiated clinically from rigidity, which is elicited by slow motion and eliminated by rapid motion, and which is most marked in the antagonists to the antigravity muscles.

It is characteristic of the spastic muscle that the motion of the antagonist is interfered with. Thus, a spastic biceps muscle has no trouble in flexing the elbow, but contraction of the triceps will cause a stretch of the biceps and thus interfere through the stretch reflex with extension of the elbow. This stretch reflex travels to all the muscles of an extremity so that mass motions of the complete extremity are elicited.

The second general group are the hyperkinesias. The muscle itself is normal, but 2 factors cause abnormality of motion: namely, the tendency for the motion to be involuntary, uncontrollable, unpredictable and often purposeless, and the tendency toward occurrence of tension. A choreiform motion is one in which the extraneous motion predominates, there being little tension. This type of motion is rapid and jerky, unpredictable and purposeless. If there is greater tension in it, it becomes a slower wormlike motion and is called an athetoid motion. When the tension becomes so great they cannot move, it is referred to as a dystonia. Such individuals develop positional attitudes; there is so much tension that it may hide the extraneous motion. In dystonia the axial muscles are more involved.

Tremor is somewhat different in that it is predictable and always the same. It is a pendular motion due to alternate action of the agonist and antagonist muscles. The direction of movement is predictable but the extent of movement not. The movement is involuntary.

Rigidity is characterized by decreased motion. In a rigidity there is disturbance in the innervation that can be found electromyographically, and when the agonist contracts, the antagonist will not relax. As a result, there is difficulty in the motion in both directions. The characteristic of this motion is greatest resistance to slow motion. In moving slowly there is a continuous resistance, involving both the agonist and the antagonist muscles. It is different from the stretch reflex, which occurs primarily in a rapid motion. Rapid movement will cause the resistance of the rigidity to disappear just like it causes the resistance of the stretch reflex to appear. This is a clear-cut differential between the two. Another difference is that whereas the spastic muscle involves primarily the anti-gravity muscle, the rigidity muscle involves the anti-antigravity muscle.

Ataxia is a balance loss, which does not necessarily involve the cerebellum alone; lesions in the frontal cortex may also result in ataxia. Thus it is better to describe it clinically as ataxia than to try to project it into pathology as a cerebellar lesion.

## CLASSIFICATION ACCORDING TO TOPOGRAPHIC INVOLVEMENT

1. Paraplegia—legs only (spastic)
2. Diplegia—legs mainly, arms slightly (spastic)
3. Quadriplegia—legs more (spastic)
   arms more (athetoid)
4. Hemiplegia—arms more (spastic)
5. Triplegia—both legs, one arm (spastic)
6. Double hemiplegia—arms more (spastic)
7. Monoplegia—rare (usually spastic)

Cases in which both legs are involved alone or to a greater degree than the arms are almost always spastics. Thus, paraplegics, diplegics and quadriplegics with greater involvement of the legs are generally spastic. Likewise, hemiplegics are generally spastic, although in this type of spasticity the arm is more involved than the leg. Quadriplegics with greater involvement of the arm are generally athetoids. In the exceptional case the quadriplegic patient with greater involvement in the arms is found in whom the diagnosis is definitely spasticity. For this type of spasticity the term double hemiplegia is employed. Generally, spasticity or athetosis exists alone and not together in the same case. In hemiplegias, mixed involvement is frequently seen, with evidence of athetosis as well as spasticity, primarily in the arm.

Monoplegias are about the rarest type of cerebral palsy. When they are seen, usually they are spastic and generally one leg is involved. In most instances where the diagnosis of monoplegia is

made, a careful examination will show involvement of either the homolateral arm or the contralateral leg. To my knowledge, in infantile hemiplegia both arms are never involved alone, although in injuries of adults such involvement is found.

### CLASSIFICATION ACCORDING TO TONICITY

Hypertonic or tension types
Normotonic
Hypotonic or "atonic" types

The tone of a patient may be increased, in which event they are referred to as hypertonic or tension forms, or it may be decreased, in which case they are referred to as hypotonic or atonic forms.

### CLASSIFICATION ACCORDING TO SEVERITY OF INVOLVEMENT

1. Mild—ambulatory and self-helpful—needs no special treatment
2. Moderate—difficult speech, self-help and/or ambulation—needs treatment
3. Severe—fully incapacitated and bed-ridden—treatment may not rehabilitate

The classification by severity of involvement is generally empiric and follows the outline given above. Many subdivisions may also be included, such as moderately severe or moderately mild, or any number of subclassifications.

### CLASSIFICATION ACCORDING TO ETIOLOGY

#### I. Anoxia

| Etiology | Clinically |
|---|---|
| Breech | Athetoids, tremors and/or rigidities |
| Narcosis | Quadriplegias |
| Maternal hypotension | |
| Cord kinks | |
| Placenta abruptio | |
| Atelectasis | |
| Mechanical obstruction, etc. | |

#### II. Trauma and Vascular

| Etiology | Clinically |
|---|---|
| Hemorrhage | Spastic paraplegia, hemiplegia or quadriplegia |
| Prematurity | Spastic paraplegia |
| Forceps or dystocia | Spastic quadriplegia or hemiplegia |
| Toxemia | Spastic hemiplegia |
| Precipitate or cesarean | Spastic or mixed |

#### III. Specific

| Etiology | Clinically |
|---|---|
| Rh factor | Athetoid with deafness and supraversion palsy |
| Internal hydrocephalus | Spastic paraplegia or diplegia plus ataxia |
| Strumpell's encephalitis | Spastic hemiplegia |
| Lethargic encephalitis | Rigidities, tremors |

On the basis of the above classifications, one may therefore describe a patient according to each of the areas mentioned above. Thus, one may speak of a severe tension quadriplegic athetoid due to kernicterus, or of a moderately severe atonic spastic diplegia associated with prematurity. Rather a large number of descriptive subclassifications may thus be used.

Some of these clinical correlates can be stated very positively, but of others there is less certainty. Anoxia, as indicated, is likely to cause an extrapyramidal syndrome—athetosis, tremors or rigidity. Because there is a specificity in the predilection of certain noxae in certain areas of the brain, it is obvious that specific clinical syndromes can be expected. Generally, those you see are pure cases. Either the child is just an ataxic or just a spastic. Combinations are not common. They are pure syndromes because they have specific etiology. If the etiology is causing severe enough involvement to involve all areas, it is likely to be fatal. The exception to the rule that cases are pure instead of

mixed is in the group of dyskinesias, in which it is the rule that athetosis, rigidity and tremors may all co-exist in the same patient.

Among the causes of anoxia we feel that breech delivery ranks high. In breech deliveries the time between the delivery of the navel and the delivery of the head is a time of potential anoxia, and if it is over 8 or 10 minutes the child will be asphyxiated rather than injured mechanically. Statistics on this show that in a large series of children with cerebral palsy, who were born by breech, the majority were found to be either spastic paraplegias or athetoids. Those which are spastic paraplegias may often be explained on the basis that the spastic paraplegia was prenatally present and the loss of the normal kicking ability in the legs made it impossible for the child to kick a presenting breech out of the pelvis. In a series of 42 children with cerebral palsy, in whom delivery was made by elective version and extraction, 40 were athetoids.

Where trauma or hemorrhage are the cause of the injury, it is most likely to involve the pyramidal tracts, since either the hemorrhages are submeningeal over the motor area on the cortex or involve blood vessels in the region of the internal capsule. Right hemiplegias are more common than left hemiplegias, possibly due to the fact that L.O.A. deliveries are more common than R.O.A. deliveries. It was interesting to note that in a series of children with spastic hemiplegia, the incidence of right to left hemiplegias was 2 to 1 in children weighing over 3.6 kg. at birth, and 1 to 1 in children weighing less than this at birth.

Spastic paraplegia is most commonly associated with a history of prematurity, presumably due to the fact that hemorrhages from the small veins entering the longitudinal sinus will be more likely to involve the leg areas than the arm areas.

In toxemias of pregnancy, the mother may give birth to a normal child or to a mentally defective child or an epileptic child, but if it has cerebral palsy it is likely to be a hemiplegic. This may be due to the fact that the child develops a prenatal stroke. What evidence have we of a stroke? Unfortunately insufficient autopsy material is available but we do have pneumoencephalograms to show tremendous hydrocephalus e vacuo and sometimes absence of a whole half of the brain. One case with a calcified hematoma on that side has been seen.

The Rh factor causes a specific type of athetoid. In kernicterus, of course, the name is derived from the fact that Schmorl noted that the basal nuclei were stained with bile. We feel that the staining of the basal nuclei occurs only in those cases where the basal nuclei have been previously injured by some other factor such as anoxia. This is indicated by the fact that newborn children with atresia of the bile ducts, where the icterus may be much deeper than erythroblastosis, do not as a rule develop kernicterus. Also, Zuelzer has shown that kernicterus is seen in premature babies who have been anoxic, and in whom jaundice later developed, in the absence of erythroblastosis.

In an attempt to determine when the insult in erythroblastosis occurs, we are doing tooth ring analysis on children who have recovered from erythroblastosis and who have sequelae. Since Dr. Shour has shown that it is possible to identify the time of birth in a tooth by the neonatal ring, it is possible to show that enamel defects occur in the teeth even before birth. This explains why the deciduous teeth of these children are generally poor, while their permanent teeth are good. This is corroborative evidence for the thinking that the brain injury in erythroblastosis begins even before the child is born.

A typical clinical picture occurs in the child who has had kernicterus. They are athetoid children with greater involvement of the neck and arms. About 30% of them have some degree of deafness, generally in the higher ranges. Over 50% of them have supranuclear lesions of the eye muscles, particularly affecting voluntary supraversion. Similar supranuclear lesions occur in the tongue muscles so that although protrusion and retraction of the tongue are generally normal, lateral motion and tongue tip raising are generally involved. That these are supranuclear lesions can be shown from the fact that synkinetically these motions which are voluntarily absent can be elicited.

(Three clinical cases were shown to illustrate the clinical syndromes of (1) kernicterus, (2) spasticity and (3) amyotonia congenita.)

*Question:* Do chicken pox or mumps during pregnancy cause cerebral palsy in the offspring?

*Chairman Perlstein:* We have had cases where there is a history of the mother having chicken pox or mumps, but certainly it doesn't occur with the same frequency that it does in german measles. It is not just the type of virus but the time of involvement. It would have to occur in the first trimester. One child, whose mother fell downstairs in the third month, has a congenital heart, deafness, spastic paraplegia, cataract and an anomaly of the brain, a syndrome which is typical of what occurs

when the mother has had german measles. The temporal factor may be more important than the specific factor. In german measles there is not a humoral immunity but a tissue immunity. The mother is able to transmit the virus in her blood without having to actually have german measles.

*Question:* Do the equine encephalitides have the same effect as measles?

*Chairman Perlstein:* The children of equine encephalitis mothers seem to have a variety of things. Some have hemiplegia but the sequelae are not the same as seen in lethargic encephalitis. During the acute phase these patients act as though they had extraneous motions, but I have not seen enough of the sequelae to speak authoritatively.

*Question:* I am from the San Joaquin Valley where we had quite an epidemic. Victims were nearly all small babies or adults. Quite a few of the adults died but we have not seen any sequelae in the babies so far.

*Chairman Perlstein:* In the lethargic group sequelae may take years to develop. As far as I know, in equine encephalitis the sequelae are immediate.

*Question:* Isn't one of the purposes of the exchange transfusion to prevent kernicterus?

*Chairman Perlstein:* According to Dr. Diamond, the reason that an exchange transfusion is beneficial is because the injury to the brain has not occurred until after birth. Diamond has also stated that his criterion for kernicterus is the development of a stiffness or back-arching in the first week. I have seen children who have not had kernicterus but have had edema of the brain or hemorrhage of the brain with the same symptoms. This might also be due to an allergic reaction from Rh antibodies. It has not been my experience that every child who shows this early clinical picture has sequelae. We all have seen children who look as though they were going to have sequelae and didn't have it. Likewise, we have seen children who had no immediate symptoms and who developed sequelae later on. We believe that the damage has already occurred before birth, though it may be true that replacement transfusion may prevent further damage from occurring. In fact, I have seen sequelae in 8 children who had replacement transfusions. You rarely see an erythroblastotic infant whose mother has 3 or 4 children after that, and the reason for the lesser incidence of sequelae is the effect of public education. Previously we would see a mother who had had 8 pregnancies and each child kept getting worse. Education is a tremendous factor. Giving transfusions is important. The point is that in the child with erythroblastosis you may not be able to recognize the sequelae for over a year because athetoid motions do not appear in these children at birth. The identifying factor in early infancy is increased tension rather than the athetoid motion.

*Question:* Would you comment on drug therapy in cerebral palsy?

*Chairman Perlstein:* I would like to say that drugs are no substitute for a training program in cerebral palsy. At best they would have only adjuvant value. The type of drugs which are used in cerebral palsy might be classed as those being of general effect and those of specific effect.

Of the drugs with general effect, one would include such things as vitamins and anti-epileptic drugs. The indication for vitamins or for anti-epileptic drugs in cerebral palsy is the same as it is for normal children. If a cerebral palsied child has convulsions, then these drugs are indicated; otherwise they are of no value. Sedative drugs, such as phenobarbital, are indicated for the same reasons that they are in normal children.

Of the drugs that are said to have specific effect on cerebral palsy, I should state the best drug that I know is alcohol. If an individual is tense, the best thing to relax him is alcohol. Many years have been spent in teaching children how to relax voluntarily and in my experience it has been a waste of time. Wine or beer may be given them. They have a specific effect in relaxing these children. The same thing may occur following anesthesia. A child who had ether for one reason or another may walk better and talk better for a week afterwards. Tridione may be effective in about 50% of the athetoid children but is less effective and more dangerous than alcohol.

Prostigmine, which is effective in myasthenia gravis, does not have too much value in cerebral palsy. In myasthenia gravis its benefit is dependent on its action on the myoneural junction; in cerebral palsy its benefit is limited to its effect upon the imagination. If an individual thinks he is going to be helped by prostigmine, he will be helped by it whether he is given the drug or a placebo. It has been proved that no better results are obtained from prostigmine than from milk sugar. In our experience it is effective in 5% of the cases, which is a very low average for a specific type of drug. Tolserol is not even as good as prostigmine. It has very little effect on an individual with cerebral palsy. This is true of the other related drugs.

Curare will actually release tension but clinically is not a good drug to use since it has a low

margin of safety and must be given by injection. Several of the newer drugs which are now under clinical trial show promise of being more helpful. Carbon dioxide (30%) inhalations also have a transient relaxing effect.

*Question:* In a very young baby, what is indicative that it might be a cerebral palsied child?

*Chairman Perlstein:* The very first thing that you would see would be a hypertonic infant. If a child has had colic, vomited and has been constipated, without any allergic cause for it or any anomaly of the gastrointestinal tract, cerebral palsy must be considered. Next you observe the child closely. How does the child hold its head up? Does this child have a smile that is differentiated? Does the child move its legs in the proper manner? Does it move one more than the other? Does it have increased tension with attempts to make voluntary movements? Actually the ability to diagnose cerebral palsy in the very young infant is directly proportional to the experience and acumen of the clinician. Since it is imperative that the clinician have an excellent knowledge of what is normal before he can recognize what is abnormal, it is obvious that the pediatrician would be best qualified to make the diagnosis early.

*Dr. McDonald:* To understand the many ways in which cerebral palsy might affect speech we should review briefly the manner in which normal speech is produced. Actually, normal speaking consists of nothing more than the making of a lot of noises. Man has learned to listen to these noises and to give them meaning. The process of making the noises is called "speech."

A study of the mechanism used in speaking shows that speech is an overlaid function and that we have no speech "organs" per se. A careful analysis of the physiologic processes which contribute to speech production indicates, however, that not only are basic biologic acts greatly modified for speech, but some functions appear to have been developed largely for speech production. Such an analysis indicates that at least 6 types of physiologic activity contribute to the speaking act: respiration, phonation, resonation, articulation, integration and cerebration.

The motive power for speech is supplied by respiration. The air which has been inhaled is held in the lungs and gradually exhaled though the larynx, where the second major physiologic event takes place. For the production of certain sounds, the vowels and voiced consonants, the vocal folds are adducted, and the outgoing air stream sets them in vibration, producing what is called "phonation." In the production of other sounds, the vocal folds are abducted and phonation does not occur; hence, these sounds are classified as voiceless sounds. The sound patterns set up at the laryngeal level are modified by resonation which occurs predominantly in the pharyngeal, oral and nasal cavities. Resonance is not only the chief factor which distinguishes one vowel from another but it affects all of our speaking by giving our voices their characteristic quality. Articulation takes place in the oral cavity where the tongue alters its position to place varying degrees of obstruction in the way of the outgoing air stream, in the case of some sounds, or to modify the size and shape of the resonating cavities in the production of other sounds. The integrating function of the central nervous system coordinates the actions of this complex neuromuscular system to produce the consonants, vowels and diphthongs [the noises] of which speech is comprised. The function of higher level processes makes it possible to impart meaning through these speech sounds.

Cerebral palsy may affect any one or various combinations of these physiologic activities which operate to produce speech. In fact, it has been estimated that about 75% of all cerebral palsied children have speech defects. Many of these children will respond to speech therapy; however, it is necessary to understand how the neuromuscular disturbance interferes with each physiologic activity before an adequate speech therapy program can be planned.

In normal respiration inhalation results from the simultaneous increase in all dimensions of the thoracic cavity. This is accomplished primarily by the elevation of the rib cage and the depression of the diaphragm. Exhalation occurs when these processes are reversed, i.e., the rib cage is lowered and the diaphragm returned to its former level. In normal quiet breathing these events alternate rhythmically about 20 times per minute with the duration of each exhalation being only slightly longer than that of each inhalation. In normal speech breathing this pattern is markedly modified. Inhalation is very rapid, occupying on the average only about one-sixth of the total respiratory cycle, and exhalation is greatly prolonged. This controlled exhalation is essential for continuous speech, i.e., speech which consists of more than one word. Cerebral palsy might produce any of several aberrations of the breathing pattern. Some children breath at a too rapid rate to be able to indulge in the vocal play which is an antecedent of speech. A too rapid rate might also prevent the prolongation of exhalation which is essential to speech production. Two types of irregularity in the breathing pattern

are often found. The child may initiate an expiratory movement of the rib cage, for example, only to have it interrupted by an inspiratory movement. This would, of course, interfere with speaking. Another type of irregularity often seen is asynchrony between the diaphragmatic-abdominal and the thoracic musculatures. Normally in inhalation the thoracic and abdominal circumferences are simultaneously increased and in exhalation they are simultaneously decreased. Sometimes the thorax and the abdomen seem to be working at counter-purposes, i.e., the rib cage may be elevating thus increasing the volume of the thoracic cavity while the abdominal musculature is pushing the diaphragm upwards thus decreasing the volume of the thoracic cavity. When this occurs the child may be unable to inhale the air necessary for speech or, should it happen during exhalation, he would be unable to produce the air stream which is the motive power of speech. Many children are observed who appear to make little or no use of the thoracic cavity for quiet or for speech breathing relying almost totally on the movements of the diaphragm for both inhalation and exhalation. It has been estimated that movements of the diaphragm alone account for only about 50% of the volumetric changes during inhalation and it is thought that a breathing pattern which does not include thoracic activity is inadequate for speech.

High speech motion pictures of the larynx, the structure which produces phonation, have shown that in normal respiration the vocal folds are abducted thus creating a triangular area through which air passes easily. For phonation the folds are adducted and placed under tension by the contraction of the laryngeal musculature. It has been demonstrated that the degree of tension is related to both the intensity and the pitch of the voice. Involvement of the laryngeal musculature may be manifest in several ways. If the vocal folds are adducted with extreme tension the child may be unable to initiate phonation. If adduction is inappropriately interrupted by abduction aspirate speech may result. Variation in tension of the folds resulting from incoordination might produce sudden changes in the pitch or intensity of voice.

The most important resonators for speech production are the cavities of the larynx, pharynx, nose and mouth. Since the size and shape of several of these cavities can be modified by muscular action it is natural to expect that disordered resonation might be a result of cerebral palsy. While it is true that cerebral palsied children often present unpleasant voice qualities this problem does not usually receive the direct attention of the therapist but rather is treated along with some of the other more serious problems.

The tone produced by respiration, phonation and resonation would be variable only in pitch, intensity and quality and would be of only limited communicative value. Articulation is the process by which this tone is modified and new sounds created to give speech intelligibility. The lips, mandible, tongue and various other intra-oral structures play important roles in articulation. For some sounds the lips are momentarily approximated and suddenly separated, for others the lips may be pursed, retracted or neutral. For 2 sounds the lower lip is brought into contact with the upper teeth. It is not enough that the child be able to perform these movements in isolation. He must be able to perform them as parts of the movement sequences which characterize continuous speech. In connected speech the mandible is rarely lowered as much as 20 ml. from its rest position yet it moves rapidly and frequently within this range to assume positions appropriate for the production of different speech sounds. Many cerebral palsied children seem to hold their lower jaws in markedly depressed positions and often they have difficulty closing their mouths. Others can open and close their mouths slowly but cannot carry out this act at the rate required for producing connected speech. Of all the articulatory structures the tongue is the most important. Consisting as it does of several muscles the tongue is able to alter its size, shape and position. Because of this facility the tongue plays the dominant role in the articulation of most of the speech sounds. Three major types of lingual involvement are seen in cerebral palsy. Of these, inability to elevate the tip of the tongue is encountered most frequently and probably has the most adverse effect on speech since it has been estimated that approximately 85% of the consonants used in continuous speech are produced by adjusting the tip of the tongue to the roof of the mouth. Athetoid movements of the tongue frequently interfere with the performance of voluntary movements and distort the speech sounds. For producing continuous speech one of the most important characteristics of the tongue is its ability to perform overlapping movements, e.g., while the tip of the tongue is being elevated the back of the tongue may be lowered. In cerebral palsy this ability to perform patterns of movement is sometimes disturbed.

It will be recognized that speaking cannot be divided into several separate activities. Respiration,

phonation, resonation and articulation are really but different aspects of the speaking process. Since speech has so many aspects it has been described as the most complicated neuromuscular act which the body performs. For the production of even a short phrase more than 50 muscles must be made to work together with precise coordination. Oftentimes in cerebral palsy this timing is upset and the patient is unable to integrate the several activities which help produce speech as a functional whole.

In the normal individual higher mental processes function to provide content for the speaker and to give meaning and coherence to his utterances. Two disturbances of these higher mental functions, both of which affect speech, are sometimes seen as concomitants of cerebral palsy. Recent research has shown that about 45% of cerebral palsied children must be classified as mentally defective. This condition not only retards speech development in the cerebral palsied but may prevent the patient from developing the level of speech proficiency of which he is neuromuscularly capable. Some children suffer a disturbance in their ability to manage the symbols of which language is comprised. The speech of these cerebral palsied children will reflect the receptive, expressive or mixed nature of their dysphasia.

The cerebral palsied child's chances of developing socially adequate speech are greatly enhanced by early treatment. It is unfortunate that the speech pathologist often does not see the cerebral palsied child until it has become obvious to the parents that the child's speech is retarded or defective. As was pointed out earlier, speech is an overlaid function which emerges from the breathing, chewing, sucking and swallowing activities of the infant. If, during early infancy, the speech pathologist could evaluate the degree to which the neuromuscular disability has involved the structures which will later be expected to produce speech he can often outline training procedures which will prepare the way for speech production. Proper seating and exercises to strengthen the head, neck and trunk muscles may improve the breathing pattern. Phonation and breathing may be improved by blowing and humming, for example. Adequate lip, tongue and jaw movements may be developed by using modified feeding procedures to improve the chewing, sucking and swallowing activities of children. Early evaluation will also provide an opportunity for the speech pathologist to advise the parents concerning proper technics for stimulating the child to speak. When early and proper attention are given to preparing the child psychologically and physiologically for speaking later attention may be given to training in the production of specific speech sounds. It is sometimes thought that it is important for the speech therapist to know with what type of cerebral palsy child she is working, i.e., a spastic or an athetoid. In our opinion it is much more important for her to know specifically what the child can do and what he can't do. Teaching the child to do those things which are important for speech production should be the objective of therapy.

*Symposium*

# NEUROLOGICAL CONDITIONS IN CHILDREN

RANDOLPH K. BYERS, M.D., *Chairman,* Boston; FREDERIC A. GIBBS, M.D., Chicago; HATTIE E. ALEXANDER, M.D., New York City; BRONSON CROTHERS, M.D., Boston; DONALD D. MATSON, M.D., Boston

## INTRODUCTION

RANDOLPH K. BYERS, M.D.

In our discussion this morning we will deal with certain neurologic conditions of childhood. Such conditions differ from those in adults in that they affect a more or less rapidly developing complex organ. You need only be reminded of the rapid increase in brain weight and of the functional maturation attending and continuing after this weight gain to realize this fact. Our various developmental and intellectual examinations are attempts at measuring the latter.

The results of disease processes may show themselves by disturbing in various ways tissues already functionally active, as for instance by suppressing respiration in the newborn, or they may injure tissue not yet mature in which case they tend to distort or suppress development. As Dr. Crothers has long maintained, recovery from acute cerebral insults in infancy and childhood differs from recovery in adult life. In the latter, approximate return to the status quo ante is a satisfactory result. If, however, a 3 year old regains his attributes as a 3 year old and then fails to continue to develop he will be feebleminded at 6. Neurologic recovery in childhood therefore requires the resumption of orderly development, and can often not be determined for a period of years after an insult.

This is not the place to attempt an etiologic catalogue of cerebral disease in childhood. Suffice it to remind you that prenatal, natal and postnatal periods of life each has its own special developmental hazards. Because these affect the developing nervous system they tend in many instances to produce rather widespread changes resulting in the functional disabilities which we label mental retardation, cerebral palsy and epilepsy. Once such holistic difficulties are established we are powerless to effect radical care.

Effective plans for the care and treatment of these chronic injuries can be made only if we have a careful assessment of the deficits and especially the remaining assets. In the very early months of life severe deficits may exist with little or no observable functional abnormality. For example a neonate with a cortical cyst in the parietal region may well show no functional disturbance at birth but at 2 months he may use the involved arm less than its fellow, and when he reaches the upright stage he will have a typical hemiplegia with reflex changes and contractures. In many instances long periods of development are necessary before any true assessment of deficits is possible.

Chronic convulsions, it seems to me, behave similarly. When they become evident early in life gross changes in brain mass or structure are more likely to be found on histologic or gross examination than is the case with chronic convulsions beginning later in life. Dr. Gibbs will consider the philosophy of the convulsive state with you.

Since we are powerless to change damage to the nervous system once it has become established it is of the utmost importance that we make every effort to prevent or minimize it during acute crises. A very commonly recurring acute crisis is that of meningitis, and on its proper handling may rest the entire intellectual and physical future of the affected child. Dr. Alexander will tell you about guides to treatment aimed at expediting recovery and insuring as well possible future development.

Unless we have some insight into the natural history of cerebral palsy we will not know whether treatment has ameliorated the motor defect nor more importantly will we be informed as to its bearing on personality development. Dr. Crothers will show you what has happened in the way of changing motor patterns and personality development in this condition in patients who have attained adulthood.

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Presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 22, 1952.

Finally Dr. Matson will call to your attention some of the very discrete disturbances of the nervous system found early in life. Again though they may be discrete, developmental and growth factors make their recognition and treatment on a surgical basis important.

I should now like to introduce to you Dr. Frederic Gibbs, Professor of Psychiatry at the University of Illinois, whose subject is "Convulsive Disorders in Childhood."

Following Dr. Gibbs, the speakers will be: Dr. Hattie E. Alexander, Associate Professor of Pediatrics at the College of Physicians and Surgeons, Columbia University, New York; Dr. Bronson Crothers, Clinical Professor of Pediatrics Emeritus, Harvard Medical School, Consultant in Neurology, Children's Medical Center, Boston; Dr. Donald Matson, Assistant Professor in Surgery, Harvard Medical School, Neurosurgeon, Children's Medical Center.

## CONVULSIVE DISORDERS IN CHILDHOOD

FREDERIC A. GIBBS, M.D.

Epilepsy is what the brain does when it is slightly injured, but the type of injury seems to be of less importance in determining the clinical outcome than the stage of development (maturational state) of the brain at the time the injury was received.

The form of the epileptic disorder varies greatly with age. Clinical and electroencephalographic manifestations must be considered together; they are but different aspects of the same thing. In the first year very severe electroencephalographic abnormality with almost continuous high-voltage, slow waves interspersed with spike seizure activity is common; this has been given the term hypsarhythmia, meaning mountainous arhythmia. The pattern denotes nearly total disorder. It is associated clinically with very frequent brief spasms, quivering spells or myoclonic jerks. Generalized convulsions occur in some cases but are not usually a prominent feature of the clinical picture. The function of the cortex appears to be so severely disturbed that there is insufficient organization to produce a series of full-blown tonic-clonic seizures. The hazard in cases with hypsarhythmia and infantile spasms is not epilepsy, but death or feeble-mindedness.

In the second to fifth year a more organized epileptic pattern is common. This consists of 2 per second spike and wave discharges; it is referred to as petit mal variant. It is usually associated with discharges of very high voltage spikes which are particularly numerous in sleep, and it is characterized clinically by frequent, short tonic and severe tonic-clonic convulsions (grand mal). Feeblemindedness is common in cases with a petit mal variant and next to hypsarhythmia the prognosis is worse than for any other type of epilepsy.

From the fifth to the twelfth year the highly organized 3 per second spike and wave of petit mal epilepsy is common. This pattern is associated with pyknoleptic seizures which have, in addition to brief impairment of consciousness, one or more of the following manifestations: fluttering of the eyelids, rhythmic (3 per second) nodding of the head or jerking of the arms and trunk. High voltage discharges of the grand mal type may be present but they are less prevalent than in petit mal variant and grand mal is a less serious complication than in petit mal variant epilepsy.

All the patterns thus far described are diffuse and more or less generalized, but with increasing age the epileptic disorder not only becomes more organized and less devastating, but more localized. For example, at ages 10 to 20 years, 14 and 6 per second positive spikes are common; these are believed to denote an epileptic focus in the thalamus or hypothalamus. The clinical manifestations are attacks of dizziness, pain, rage and vegetative disturbances but tonic-clonic convulsions occur in approximately 50% of cases. In adult life the epileptic pattern that is most common is a focus of seizure activity in the anterior part of the temporal lobe. A high percentage of patients with this type of focus have major convulsions, but the pathognomonic clinical feature is confusional attacks or trance-like episodes with coordinated and more-or-less purposeful movements.

Although focal epilepsy is less common in infants and children than in adults, epileptic foci occur at all ages. In infancy the most common focus is in the occipital areas, in childhood in the mid-temporal areas and as previously stated the anterior temporal focus is the characteristic focus of adult life.

Discrimination and understanding are aided by viewing the clinical and electroencephalographic aspects of epilepsy in combination, over a time range that permits consideration of maturational changes. This view suggests that the form which epilepsy takes is largely determined by the age (maturational state) of the brain when the injury was sustained. Although certain types of injury are more common at certain ages than others a great variety of different types of injury are capable of producing the same electroencephalographic disorder and the same types of clinical epilepsy.

## GUIDES TO OPTIMAL THERAPY IN BACTERIAL MENINGITIS

HATTIE E. ALEXANDER, M.D.

It is now apparent that the potential 100% recovery rate from the commonly occurring varieties of pyogenic meningitis is far from being realized. The limitations of therapy over the past 10 years are documented by a number of reports of a significant incidence of sequelae of neurologic and psychologic nature. The frequency of subdural collections of fluid as a complication during recovery from pyogenic meningitis has been reported from a number of institutions. These limitations are apparently the result of late diagnosis, both clinical and bacteriologic, and suboptimal use of the available therapeutic agents.

The goal—100% recovery—can be approached only if we aim for optimal therapy. This paper will present the guides which are of value in attaining optimal therapy. In the process 2 controversial subjects will be discussed: indications for intrathecal therapy, and the use of certain combinations of antibiotics. Four principles can serve as guides to optimal therapy.

I. For therapy to be optimal, it must be applied early in the course of the disease.

II. The organism must be eliminated in the shortest possible time. A number of guides are useful in attaining this aim.

A. Use of 2 agents which work through different mechanisms of action to prevent emergence of resistance. The available knowledge on this subject is summarized.

B. One of the agents used should, if possible, be primarily bactericidal.

C. In order to obtain the most rapid elimination of the infectious agent, bactericidal concentrations must be attained rapidly in the spinal fluid and constantly maintained over a long enough period to kill the organisms during their first exposure.

III. Intrathecal therapy should be kept at a minimum.

The aim to reduce intrathecal therapy to a minimum is occasioned not by evidence that patients are damaged by reasonable doses intrathecally, but by the fact that it is now unnecessary except under the circumstances outlined.

IV. Agents which may injure patients are to be avoided if others which are safe are equally good.

It is now possible to avoid to a large degree agents which may injure the patient, such as streptomycin, polymyxin B and bacitracin. Only in tuberculous meningitis are we justified in accepting the risk of damage by the usual streptomycin therapy.

## THE LONG-TIME PROGNOSIS OF CEREBRAL PALSY

BRONSON CROTHERS, M.D.

For the past year we have been recalling individuals with cerebral palsy who have been seen on the neurologic service or in private practice, since 1925.

All cases have been seen by one physician or his close associates, all psychologic testing has been done under the supervision of one of 2 psychologists, and all physical therapy under the supervision of one individual.

Whatever is good or bad in this situation, one thing is clear. All mistakes are our own, and we know pretty adequately our own attitudes. We started off with a few convictions which we still cling to.

First we always recognized that we were dealing with a physiologic and psychologic problem in a growing and developing child. We were also aware that the family, the school and later the industrial opportunities had a very definite effect upon the patterns developed as years went on.

Furthermore we accepted very quickly the idea that psychologists could help us more than psychometrists.

A follow-up study of this sort ought to be concerned with several aspects of the problem:

1. The validity of the original appraisal. In this connection we have been interested in the possibility that unexpected changes may be due to anatomic changes as time went on.

2. The possibility is obvious that a reappraisal might throw light on the validity of various methods of treatment.

3. The emotional, economic and educational costs can be correlated with the efficiency of the individual in adult life.

4. Revision of methods of examination might be suggested.

In this symposium 3 moving pictures were shown. In one, a series of pictures at various ages

show the difficulties of an alert child with severe cerebral palsy and tonic neck patterns. At first the child appears to share the optimism of the therapist. As time goes on, less enthusiasm for the imposed activity is evident.

The persistent tonic patterns finally convinced the medical part of the group that the child would not benefit by further pressure. Finally her status in young adult life is shown with her assets and deficits clearly defined.

It is our hope that a series of such observations may clarify some of the problems we all see.

Another aspect of the study was illustrated by 2 pictures, showing methods of establishing the pressure of hemianopsia in children. We were lucky enough, a year ago, to enlist the interest of Dr. J. P. M. Tizard, of St. Mary's Hospital, in London. He found hemianopsia in a large number of the hemiplegics that returned for study. Many of these children had been recognized as hemiplegics in infancy, but sensory studies had not been done then, or later.

The hospital has under observation a considerable group of young children so that it was possible to find appropriate hemiplegics at various ages. The method of Dr. Tizard is illustrated by a film showing the co-operation of a borderline defective at 12 years. A second film, of a defective restless child of 5 years, shows another method of demonstration which involves selection of toys presented at equal distances from each side. These films shown, of course, are of interest only because they show the relevant activities of children at different ages.

As we go on with this study, we will attempt to continue the rather laborious follow-up of cases and hope for further disconcerting experiences which will lead to review of our technics with younger children. Certainly we have been taught to look for sensory disturbances and to appreciate their importance.

## DEVELOPMENTAL ANOMALIES OF THE NERVOUS SYSTEM OF SURGICAL SIGNIFICANCE

DONALD D. MATSON, M.D.

There is a new type of surgery practiced today in an ever increasing degree; this is prophylactic surgery directed toward the prevention of the complications of congenital defects. Two types of congenital disorders involving the central nervous system are selected for discussion because they are rather poorly understood and because, when promptly and properly diagnosed, they are subject to surgical treatment with gratifying results.

The first of these consists of congenital dermal sinuses with persistent intracranial or intraspinal extension. When there is failure of both mesodermal and ectodermal structures to fuse properly in the midline, dermal sinus tracts may extend all the way into the central nervous system, particularly in the suboccipital and lumbo-sacral regions. Here the sinus may become attenuated in the meninges or it may expand to form an epidermoid or a dermoid cyst. Such a cyst may act as any other expanding lesion to interrupt function by local compression or by obstruction of spinal fluid circulation. It also acts as a persistent portal of infection from the skin surface.

The results of surgical treatment prior to infection have been uniformly gratifying; the results of treatment when the proper diagnosis was made only after meningitis or abscess formation occurred have been extremely poor. This lesion should be suspected whenever there is a midline skin dimple or sinus tract opening and particularly if there is an underlying defect in the bone of the skull or spine on x-ray examination. A history of meningitis or physical signs of increased intracranial pressure or spinal cord compression associated with such a skin defect are practically pathognomonic.

Such a sinus tract should not be probed or injected. The treatment of choice is complete excision of the entire dermal sinus tract together with all cystic expansions wherever they may extend, before infection has occurred or at least at a time when no active infection is present. This usually means posterior fossa exploration for the intracranial lesions and laminectomy for the spinal lesions.

The second congenital disorder is an unusual but constant type of spina bifida occulta in which the distinguishing feature is the projection of a discrete bony spicule from the posterior surface of a vertebral body through the center of the spinal canal, thus dividing it into compartments and transfixing the spinal cord or cauda equina. These patients are designated by the term diastematomyelia, signifying a cleft or division of the spinal cord. It is important to correct this disorder during the period of active growth of a child to prevent progressive loss of function.

These bony spicules have been seen at various levels from $T_8$ to $L_4$. They may be suspected by

an overlying cutaneous abnormality such as excessive hair growth, a skin dimple, a subcutaneous fat pad, or cutaneous vascular malformation. The lesion is usually discovered during investigation of a gait disturbance, lower extremity deformity or impairment of bladder or rectal sphincter control. Roentgenographic findings are characteristic, showing a widened spinal canal, spina bifida, and the midline bony spicule.

Treatment consists in surgical excision of the bony spicule, division of the numerous fibrous adhesions between the septum and the split cord, and conversion of the reduplicated spinal canal into one channel. This has repeatedly resulted in clinical improvement and almost always in an arrest of any advancing neurologic abnormality.

These 2 lesions are illustrative of conditions in which well conceived and carefully performed surgical procedures can do much to prevent progressive disability and perhaps disastrous complications and should, therefore, be recommended strongly as elective procedures.

Pediatrics

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## SPECIAL SECTIONS

# THE PEDIATRICIAN AND THE PUBLIC

*"A forum where discussion could be free, intelligent and continuous."*

PAUL A. HARPER, M.D., *Editor*

*Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.*

Dr. Osler Peterson, the author of this communication, is a native of Minnesota, who as a staff member of the Rockefeller Foundation has been their representative in Great Britain. After two years of observation he wrote *A Study of the National Health Service of Great Britain* to provide reading material for visitors who came to learn about the Service. This study was first produced in mimeographed form, but the demand was so great that it is now being issued as a book. The mimeographed edition received high praise in a *Lancet* editorial as an impartial, critical and fair review of the National Health Service; it is the best exposition of this subject which this editor has read.

## NATIONAL HEALTH SERVICE OF GREAT BRITAIN

*By* OSLER L. PETERSON, M.D.

IT IS scarcely necessary to call attention to the enormous social changes of the past decade and their effects upon the practice of medicine. In the field of medical care we have seen the truly astonishing growth of Blue Cross hospitalization insurance and more recently the equally remarkable expansion of voluntary medical care insurance, as typified by Blue Shield as well as other plans. There is also the greatly expanded veterans' service providing extensive tax-supported medical care for a large fraction of the population.

Even though it is now possible for most American families to insure themselves against the expenses of medical care, no one would claim that all our problems are solved. Change is continuing, and more changes are inevitable. It is not suggested that we can borrow techniques or methods from other countries. Some procedure that works well in one country may produce indifferent results in another. It seems probable that by studying the National Health Service of Great Britain or similar services in any other country we should be more aware of the implications of the changes occurring in our country.

Britons and Americans often assume that they are very much alike because they speak similar languages and share certain ideals. For this reason it would be well to review some of the background of the National Health Service to emphasize some of our differences.

Indeed, if one were to understand the National Health Service, it would be necessary to discuss many British social institutions and show generally how these differ from ours in the United States, but space precludes this. Voluntary sickness insurance began in Great Britain before 1900, with the formation of sickness clubs which paid doctor bills for their members. These clubs were based upon trade unions, religious, fraternal, social, or other groups, to which the individual members made weekly contributions. In 1911 the Liberal Government, under Lloyd George, consolidated these many sickness clubs into the National Insurance Service. The sickness clubs were allowed to continue as insurance carriers, with the government providing a floor under the benefits provided by the individual clubs. There was an income ceiling on membership, but for practical purposes it can be said that National Insurance ultimately covered all employed persons in Great Britain, or almost half of the population. Hospitalization was provided by either the voluntary hospitals or the local authority hospitals, with charges adjusted to the patient's ability to pay. Although the various sickness clubs, which acted as insurance carriers, provided markedly different fringe benefits and varied equally much in their administrative efficiency, the medical profession appeared to have been reasonably well satisfied with the insurance principle involved and the capitation systems of payment. The medical profession's acceptance of this form of insurance is best attested by the fact that the British Medical Association in 1930 and again in 1942 recommended the extension of coverage to include virtually the whole population. The well-known Beveridge report of 1942 did not recommend a National Health Service but made the assumption that its program of disability and old age pensions, unemployment, and other benefits could be operated only in a society with active public health, medical, and rehabilitation services, capable of preventing much disease, treating patients promptly, and returning them to work at the earliest possible moment. In 1944 the coalition government headed by Churchill issued a White Paper in which the government committed itself to setting up a National Health Service in the postwar period. The 1946 act which ultimately created the National Health Service was a product of the Labor Government and somewhat more extreme in its provisions than that proposed by the previous government or than the medical profession had expected. It is largely on the basis of the Labor Party's additions to the previous plans that objections have come from the medical profession.

Though the insurance principle was retained in setting up the National Health Service, the individuals' contributions provide only a small fraction of the funds necessary to its operation. The largest part of cost of the National Health Service comes out of general tax funds; in effect, the medical services were nationalized. Under the National Health Service each person can select a personal physician who will care for him without direct charge. His physician can prescribe medicines or appliances, refer him to a specialist or hospital or any personal health service. These services are supplied entirely on the basis of the patient's needs without direct payment.

## The Hospital Service

The National Health Service is composed of three major divisions, all of which are responsible to the Minister of Health, and through him to Parliament. The largest of the three divisions of the National Health Service is the nationalized hospital service, which has taken over virtually all of the hospitals of the country. The regional boards and the management committees are responsible for the provision of all types of hospital care, including that in general acute bed, tuberculosis, and mental institutions. They not only provide for administration and maintenance of the hospitals but are also responsible for the provision of specialist medical staff, nursing, technical, or other services usually found

in hospitals. Except for the few persons who elect to remain as private patients, these services are supplied to the individual on the basis of medical needs without direct charge. England and Wales have been divided up into 14 hospital regions in such a fashion that each includes at least one medical school. Each of these regions is the responsibility of a regional board of 25 members appointed by the Minister of Health. The duty of this board is to plan and supervise the services of its area and to appoint medical staff for the constituent hospitals. Regions vary in size from just over a million to over four million persons. These regions have been subdivided into management committee areas, of which there are 377 in the country. The hospital management committees, which are appointed by the regional hospital boards, are responsible for the day-to-day administration of a hospital or, more frequently, of groups of hospitals, usually totaling 1,000 to 2,000 beds. Management committees, like the regional boards, are composed entirely of voluntary workers. Both have full-time, paid executive staff. Medical staffs of the hospitals are composed almost entirely of specialists or specialists in training and are paid by salary. Appointments are made by a medical committee of the regional hospital board. The boards are, in fact, heavily weighted with physicians. The medical committees expend a great deal of time and effort in making the appointment to the individual hospital, with the result that well-qualified specialists staff the hospitals throughout the country.

Before the hospitals of the country were taken over by the Ministry of Health, there were great regional variations in the quality of hospital buildings, equipment, and staff, reflecting local resources. In the wealthy southeastern part of the country one found better equipped and staffed hospitals than in the midlands where one found proportionately fewer beds in less satisfactory buildings and with a poorer quality of staff. The postwar housing needs of Great Britain have been so acute that any program of hospital building has been impossible, but many of the qualitative differences have disappeared. The midlands may have few more beds now in relation to its population than before and may have fewer than a wealthy residential suburb of London, but within these restrictions great improvements have been made. Well-maintained, well-equipped and well-staffed hospitals are now available in parts of the country where such was not the case before the National Health Service. The success of the hospital organization can be attributed to several factors. Much attention has always been given to hospital administration, so there were knowledge and experience upon which to build. Excellent models existed in the teaching hospitals for organizations that would encourage the best quality of medical staff. With this background, an organization was set up to plan and provide a good quality of hospital care. Lastly, sufficient money has been allocated to make possible the provision of adequate staff, equipment, and maintenance. The hospital system is far and away the most expensive of all the branches of the National Health Service. It consumes somewhat over two-thirds of the more than four hundred million pounds ($1.16 billion) spent annually on the National Health Service.

Although each region was so drawn as to include at least one medical school and its teaching hospital, the latter has been given an independent organization. The teaching hospital is controlled by a board of governors responsible directly to the Minister of Health, and the medical school continues to be a university responsibility. In general, the teaching hospitals have been able to expand their clinical facilities by absorption of neighboring hospitals. The inclusion of medical school in each region was clearly a device to aid in maintaining the quality and skill of hospital staffs throughout the area, as well as in providing highly specialized services that are likely to be available only in medical schools. The autonomy of the teaching hospitals appears to have isolated them from the

other hospitals. In Scotland, where teaching hospitals were included as integral parts of the regional organization, the universities' influence upon quality of work in general hospitals appears to have been great.

## The General Medical Services

The second major division of the National Health Service is the general medical services. Executive councils based on local government areas and appointed by the Minister of Health, the local government unit, and the practitioners concerned are responsible for provision of general medical practitioner, dental, pharmaceutical, and ophthalmic services for their local areas. These councils are executive agencies and are not responsible for formation of policy in any sense. Much of their administration is done in conjunction with local committees which represent the profession concerned. For example, the local medical committee and the executive council deal with the local problems of general practice. Similarly, local dental, pharmaceutical, and ophthalmic committees deal with the various local professional groups. The professions have clearly been given a great deal of responsibility for their own affairs.

The Family Doctor Services: The vast majority of general practitioners in Great Britain have chosen to enter the National Health Service, and similarly the vast majority of the people of Great Britain have chosen to obtain their medical care through it. Every person in the country is expected to choose a family doctor. Up until very recently a doctor has been paid 18 shillings, or approximately $2.50, annually for each person who registered with him. Limitations were placed upon sizes of lists which general practitioners might have. In the case of a practitioner working alone this was 4,000 persons. In addition to the capitation payment, doctors in rural areas are given substantial mileage payments in proportion to the average distances which they must travel to see their patients. Before the National Health Service, entry into general practice was usually by means of sale and purchase—a form of insurance maintained by custom and the prestige of the British Medical Association. Doctors have been compensated for the loss of their investment at about the accepted sale rate. The prohibition of this method of entry has necessitated a new mechanism for placing doctors. This is the responsibility of a national Medical Practices Committee composed largely of general practitioners. This committee theoretically can control entry into general practice, but its powers are limited to closing "over-doctored" areas to new entrants. The London Borough of Hampstead, which had one physician per 250 persons in 1948, is in this category. In other areas, a practice which becomes vacant is widely advertised in the medical press by the local executive council, which also selects a successor subject to confirmation by the Medical Practices Committee. Neither can prevent an unsuccessful candidate from purchasing the retiring doctor's office. As in the case of the military situation, he who gets there first with the most also gets the decision. Where there is a partner or assistant or other logical successor, a practice is routinely given to him. The closing of the obviously over-doctored areas and the fact that doctors can now make as good a living in poor areas as anywhere else is slowly affecting a redistribution of doctors in relation to population.

The British Medical Association's publication, *The Medical Practitioner's Handbook*, states in its introduction, "It should be appreciated that there is free choice of doctor by patient and of patient by doctor, this being one of the essential freedoms upon which the profession insisted when the National Health Service Act came into operation." The doctor contracts with the local executive council to care for the patients on his list. His agreement with the council covers his obligation to give due and proper care "within his competence" and is in no way more than a doctor's normal obligation to his patients.

In effect, the executive council is mainly an agency for paying the general practitioner and maintaining the usual bookkeeping services in the cases of patients registered with him. It should also be pointed out that patients may change doctors at any time and that the doctor may request a patient to change to some other doctor whenever he wishes. The relations of the general practitioner and his patients are very much the same as they would be under private practice, with the exception of the fact that he is now paid by the national government. Doctors may do private practice, though the number of persons who choose to remain as private patients appears to be so small as to be unimportant. It is quite apparent that the general practitioner has been allowed to retain almost complete freedom to practice medicine as he did before the National Health Service. This is both good and bad. It is good insofar as the doctor's freedom is essential to the practice of medicine and the maintenance of the doctor-patient relationship. It is bad insofar as almost nothing has been done to encourage good general practice.

There has been in Great Britain, generally speaking, a division between general practitioners and specialists. Specialists have always worked in hospitals or in a consultant capacity to general practitioners; the latter have usually worked outside of hospitals. Though some general practitioners did have access to hospital beds before the National Health Service and continue to today, the numbers who have such privileges appear to be small. While figures have never been published, it would seem from budget estimates of payments made to general practitioners for hospital work, that not more than 2% of the hospital beds in Great Britain may be under general practitioner control and that not more than 15% of general practitioners may have hospital connection. It will be recalled that one organization was set up for hospitals and a completely separate organization created to administer general practice. This administrative separation of doctors into two types has resulted in their functional segregation into two widely separated groups. Most hospitals have been run as though hospitals existed for their own ends and without relation to the general practitioners who may surround them and supply them with patients. Typically, the consultant in the hospital will state that he does not want to have general practitioners performing services in the hospitals, since he must protect the quality of service that is being given. For similar reasons laboratory services have not in general been made available to the general practitioner by the hospitals. In consequence, we have the general practitioners working throughout the country with limited facilities and often in isolation. The continuity of medical care, which it was hoped the provision of a family doctor service would provide, has had severe limitations placed upon it.

It is further evident that the number of patients permitted to each practitioner is too high. There are, as an average, between 2,400—2,500 persons per general practitioner for all England and Wales. Some doctors are young, others are old, some serve as part-time factory doctors or otherwise limit their practices, so such an average means almost nothing. The Minister of Health recently gave the figures below, showing the distribution of doctors by the size of their lists.

| No. of Doctors | No. of Patients |
|---|---|
| 2,400 | under 1,000 |
| 1,613 | 1,000-1,500 |
| 1,936 | 1,500-2,000 |
| 4,059 | 2,000-3,000 |
| 5,916 | 3,000- |
| Total 15,924 | |

(Attention should be called to the fact that these figures are incomplete since there are almost 19,000 general practitioners.)

The author has visited many general practices, and it is clear that no doctor working solo can adequately care for 4,000 patients, the statutory number permitted. It is doubtful if he can easily cope with 3,000, but it seems that it is possible to give careful, unhurried care to 2,000 or slightly more patients under conditions of the National Health Service. It appears now that a recent augmentation of the general practitioners' remuneration by about 25% will be accompanied by a reduction in the maximum permitted list as well as a method of payment that will allow proportionately more pay for small lists than for large ones.

It is probably clear from the foregoing that the general practitioners have been dissatisfied with their role in the health service. This is probably due to many factors, including isolation, public criticism of general practice, and the conditions of practice itself. Although their pay and the amount of work they do is related directly to the number of their patients, many doctors seem to feel that they have no control over their practices. In any given day a doctor may be called upon to treat 20 or 40 or 60 patients, while he has lost his conventional assurance in the form of a fee that the patient takes his visit seriously.

When the National Health Service was set up, the consultants had no difficulty in accepting it. They were offered professional freedom, tenure, good pay, and excellent conditions under which to work. The British Medical Association, as the spokesman for the general practitioners, fought hard for professional freedom. This was commendable, but in retrospect it appears that this issue was never seriously in doubt. The government was as eager as the doctors to conserve the historic character of the doctor-patient relationship. The Association might have saved the general practitioners many problems and much criticism if it had fought for conditions of service that would not only have permitted but also encouraged quality in general practice.

Dental Services: Executive councils also make provision for dental services. There are approximately 10,000 dentists in Great Britain, whereas it is estimated that the country would need 20,000 to provide adequate services. In view of the known shortage of dentists, it was decided that payments would have to be on a fee for service basis. The general philosophy of the National Health Service dictated that dental treatment be free. Patients thus had every inducement to seek treatment, and dentists had every inducement to do as much work as possible. The author has been repeatedly told by competent dentists that British teeth are among the worst in the world, an opinion with which one would concur on the basis of casual observation.

Three factors in combination have produced an almost explosive mixture. The enormous demand, the large amount of service, and public indignation have grown apace. The history of the dental service since the inception of the Health Service in 1948 has been the history of repeated reductions in fee payments and more recently of the imposition of a charge for some dental services. To date no figures have been published on the effect of imposing such charge, but it is believed that it has resulted in a marked reduction in the demands for dental services.

Pharmaceutical Services: A third duty of the local executive council is the local provision for supplies of drugs and appliances. Since "chemist shops" are about as ubiquitous in Great Britain as drug stores in America, no new service was created. The patient obtains medicine by presenting his prescription at the pharmacy. Until recently all appliances and medications, important and minor, were supplied free to the patient. The enormous national drug bill that resulted has made for popular dissatisfaction with this branch of the service. While the size of the drug bill may be determined largely by the

factors mentioned above, conditions of general practice may also contribute to it. It is interesting that in Sweden, where most of the local sickness funds supply important medications only (e.g., penicillin and insulin but not aspirin or tonics) to insured persons, little complaint is heard. Most British general practitioners have between 3,000 and 4,000 patients to care for, a number clearly incompatible with careful, deliberate, and unhurried care to the individual. A recent investigation of prescriptions has shown that the general practitioners are prescribing phenobarbital and other sedatives more frequently than other type or class of medication, which would seem to substantiate the thesis that general practitioners do not have time to deal adequately with the bulk of their patients.

Supplementary Ophthalmic Services: The fourth service provided by the local executive council is the supplementary ophthalmic services, which includes ophthalmologists, opticians, and other groups involved in supplying spectacles.

## The Public Health Services

The third major division of the National Health Service is the public health services. These have been changed very little in form as compared with the period before the National Health Service. They were then operated as functions of the local government units, and they continue in this role. Before the National Health Service, the local medical officers of health were responsible for the administration of the local government hospitals. Since the hospitals have been transferred to a new agency, the major effect of the Health Service has been to reduce the medical officer of health's responsibility considerably.

The development of maternal and child health services is much greater in Britain than here. Before 1948 the majority of antenatal and well-child care was given through the public health clinics which have been widely provided in all local government units. Deliveries in most cases were performed by the highly trained nurse-midwives who are also members of the public health department. Most general practitioners did little or no obstetrics, but in setting up the National Health Service it was reasoned that they should take care of their patients through the period of pregnancy and delivery as well as provide well-child care if they were to become "family doctors." They were therefore given a special fee for caring for pregnant women. In Great Britain as in the United States there has been a marked increase in hospital deliveries. The inducement offered to general practitioners to do obstetrics, together with the popular trend toward hospital confinements, has been decreasing the local public health services' work in this field quite sharply.

The maternal and well-child care situation highlights the major problems of the health service, i.e., the division of responsibility for the individual patient. It can be seen that a pregnant woman may easily come under the administrative responsibility of any or all of the three major divisions of the Health Service during her pregnancy. The public health clinics are extensively developed and as they are available to virtually the whole population, in the past, two-thirds or more of the women obtained some prenatal care through them. The cost of these extensive services is about one-fifth of the cost of the general practitioner service. It is pertinent to question if they are necessary when everyone has a family doctor. This question will probably be asked with increasing frequency since the attendances at the antenatal and well-child clinics have declined quite sharply since the beginning of the National Health Service.

## Discussion

It is hoped that the foregoing brief description of the National Health Service will provide in barest outline an understanding of its organization and administration. There are a number of other important points which would certainly be of considerable interest to American doctors. Certainly, one of the foremost of these would be the question of what effect the National Health Service has made on the amount of work being done by doctors. In the case of the hospital the figures available are subject to such considerable limitations that it is difficult to say what increase, if any, has occurred in the amount of care given. Due to the nursing shortage, which is due, in turn, both to the low birth rate of the 1930's and to the present period of full employment, there are some closed hospital beds which must be balanced against beds added during the war years. It appears that the hospital beds in Great Britain before the war were filled to capacity at all times and that there was a constant waiting list for hospital admission for many types of patients. These included, particularly, patients in need of elective surgery and some patients with chronic disease. The hospitals under the National Health Service are continuing to operate at capacity, and the waiting list appears to be constituted now as it was formerly. The average length of stay in hospital is decreasing just as in the United States, so it is probably safe to assume that hospital care being given today is not grossly different in amount than that given before the National Health Service. It might be mentioned parenthetically that there are approximately five general hospital beds (this including chronic disease) per thousand population—a number somewhat greater than we have in the United States. It is clear that the patients' needs for acute hospital beds are being met by and large. There are not sufficient beds in the field of tuberculosis, though here the number of deaths is declining so rapidly that it would appear that the facilities will soon be in balance with the need. The other area in which deficiencies exist is in the beds for chronic disease. As in the United States, there is in the British population an increasing proportion of older people, with a consequent increase in the amount of chronic disease. The pattern of full employment and the many other social changes that have come about in the last two decades are making it extremely difficult to care for patients in the home—with a result that demands for hospital beds are high.

The Ministry of Information's social survey organization has been conducting a continuous survey of sickness and medical consultations, which gives some information about the general practitioners' load of work. In the first year of operation of the National Health Service the numbers of visits to doctors increased some 13% over the year preceding its inception. The increase in visits to doctors was largely among women, and particularly elderly women, previously uninsured. The figure of 13% would not indicate that the demands for medical care have increased enormously, though it must be recognized that this increase has probably occurred irregularly throughout the country. It seems very likely that in the poorer areas the increase has been substantially greater than in relatively prosperous rural areas. In fact, rural doctors in general state that the Health Service made little difference in their practices, while the doctors in the industrial areas are likely to say that they have become impossibly busy. It was noted before that the distribution of general practitioners is improving with the operation of the National Health Service. Recently the general practitioners' demand for better pay was carried through the government arbitration machinery, with the result that substantial increases were awarded to them. In view of these increases, the British Medical Association has proposed a different method of payment which would discourage doctors from caring for a large

list and has also proposed a reduction from 4,000 to 3,500 in the number of patients permitted on any single doctor's list. It seems very likely that this proposal will be accepted by the government.

There are other points which we can very well study in the British services. The historic separation of specialists and general practitioners in Great Britain, which was formalized in the National Health Service, has fortunately never been the general American pattern, though closed hospital staffs are not rare. In this country the hospital is regarded as the doctor's workshop and not as the workshop of the consultant or specialist only. The association which the doctor forms in the hospital with his colleagues and the facilities which are available there are certainly of considerable importance to the individual doctor in maintaining his skills and important to society in maintaining the quality of medical care. One of the great misfortunes of the National Health Service has been that it has done nothing to improve the quality of the doctor responsible for providing most of the medical care for the bulk of the people. It should be pointed out in this connection that voluntary health insurance in America has begun by making provisions for hospital service and has succeeded in a far smaller degree in making provisions for a family doctor service. One may ask whether the emphasis in this case may not indicate that we are in some measure and in a different setting falling into errors similar to those which have plagued British services.

A third point of considerable interest is the problem of democratic control of health services. As the reader has seen, some health services are locally administered by the local government, and in others an important voice is given to the professions concerned. In the case of the hospital, administrative responsibility has been highly centralized. The day-to-day administration of the hospitals by the appointed management committees is concerned constantly with fiscal problems. Since nonelected bodies in Britain are not given discretion in spending public funds, many decisions as to local financial practice cannot be made by the local management committee or even by the regional board. These decisions must be referred to the Ministry of Health or even to the Treasury. This disassociation of authority and responsibility must be very exasperating to the many able people who give much time without pay to running the hospitals. Such long-range responsibility will not be unfamiliar to medical administrators in our state and national government. It is widely held in the democracies that decentralization of functions is desirable in the interests of having citizens take responsibility for their own welfare. In the operation of a local hospital or any other services whose effects are so personal and intimate as medical care, such local responsibility is doubly important.

It is not surprising that a change as complete as the institution of a National Health Service, with the almost infinite number of molecular adjustments which such a revolution requires, cannot be described in terms of success or failure. Some parts such as the hospitals are better in proportion to previous experience with hospital organization and to the effort expended in assuring improvement. General practice, though different, is probably neither better nor worse. Much attention is now being given it, and as experience is accumulated it can be expected that improvements will be made.

In our own country the veterans' administration certainly represents one of the largest medical care programs. Its hospitals have characteristically given excellent medical service, but in terms of providing continuity of care, local democratic control, and patient responsibility, it appears unsatisfactory. This is but one of the many changes in medical care that are going to make great demands upon the wisdom of an informed medical profession in America in the next few years.

# NEWS AND ANNOUNCEMENTS

## SPECIAL THREE DAY COURSES IN CLINICAL RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

The Committee on Rheumatic Fever and Cardiac Disease of the American Academy of Pediatrics has assisted in the organization of short courses in rheumatic fever and rheumatic heart disease for pediatricians. In response to this effort 2 special courses will be offered in the spring of 1953. Major emphasis will be given to the clinical aspects of the disease, a minimum of didactic lectures and a maximum opportunity for case studies, auscultation, fluoroscopy, interpretation of electrocardiograms, etc.

New York University Postgraduate Medical School: April 15, 16 and 17, 1953, daily 9:00 a.m. to 4:00 p.m. Minimum enrollment 8, maximum, 16. Fee: $35.00. For information or enrollment, address: The Associate Dean, New York University Postgraduate Medical School, 477 First Avenue, New York 16, N.Y.

University of Pennsylvania Medical School, The Children's Hospital of Philadelphia: April 24, 25 and 26, daily 9:00 a.m. to 5:00 p.m. Enrollment limited to 10. Fee $35.00. For information or enrollment, address: The Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46.

# EDITORIAL

## SHOE-FITTING FLUOROSCOPES

THE dangers of radiation have been recognized for many years. Even experienced physicians use x-ray equipment with extreme care and only when benefits from diagnosis and treatment can be expected to outweigh possible harm.

It is not surprising, therefore, that roentgenologists and public health departments have become increasingly disturbed over the use of x-ray shoe-fitting machines in retail shoe stores. The New York State Department of Health and the New York City Department of Health have recently altered the Sanitary Code in order to regulate the use of fluoroscopes in shoe stores. In Detroit, and many other parts of the country, health authorities have also attempted control measures for reducing the radiation hazard potentials inherent in the use of these machines.

Health departments are concerned with the radiation danger to both customers and store personnel. Pediatricians will be concerned primarily by the fact that these machines are most widely used in fitting children's shoes.

Growing bone is easily damaged by exposure to x-rays. Damage is shown by reduction in the rate of bone growth and by premature closure of the epiphyseal junction. Animal studies have shown that the younger the animal, the greater the effect on bone growth of a given dose of x-rays.[1]

During the last few years a movement to regulate the use of x-ray machines for shoe fitting has become active. Nontechnical as well as many professional articles have appeared on the radiation hazard potentials of these machines. A number of studies have been made of the machines under conditions of actual use.

The movement began gathering momentum around 1946 when the American Standards Association set 2 r per exposure (to the foot) as the permissible limit for shoe-fitting fluoroscopes in its *Safety Code for Industrial Use of X-Rays* (A.W.S. Z-54.1).[2] In 1948 the American College of Radiology printed a discussion of the dangers of fluoroscopic shoe fitting in its February *News Letter*. A few months later, two of its members, Dr. G. C. Henny and Dr. F. E. Hoecker, presented measurements of machines made in two cities. They showed cutoff times varying from 12 to 27 seconds and dosage rates from 10 to 140 r per minute, all far above the recommended standard for safety.[3]

Following this study, a warning editorial appeared in the April 9, 1949, issue of the *Journal of the American Medical Association*. Later the same year the *New England Journal of Medicine* presented a report by Williams[4] on radiation exposures from shoe-fitting machines and one by Hempelmann[5] on radiation's potential hazards, which he summarized as follows:

> "It may be said that the type of radiation injury most likely to result from unsupervised use of low-voltage fluoroscopes in shoe stores is the malformation of the feet of growing children. Such deformities may occur in the absence of x-ray reactions of the skin."

Danger arises from too high an intensity, uncontrolled length of exposure, or repetition of exposure. Even when the first two dangers are controlled by safety devices on the machine, as some manufacturers have done to protect both customers and store personnel,

there is still danger to customers of uncontrolled repetition in trying on other pairs of shoes, and in shopping from store to store.[6]

In addition to the hazards of radiation, there is a question whether fluoroscopic examination is in the least helpful in fitting shoes. Shoe salesmen interviewed in one study considered the machine a sales promotion device rather than a fitting aid. The Committee for Study of Radiation Effects in Childhood of the American Academy of Pediatrics concurs. In a report to the Executive Board of the Academy of Pediatrics, via the Children's Tumor Registry, it recommended that "the use of fluoroscopic machines for the fitting of shoes of children should be strongly discouraged or prohibited for the following reasons:

1. There is no evidence that the use of such machines aids in accurate shoe fitting. The visualization of the soft parts is usually quite poor and the interpretation of the entire view of the bones of the foot is made by a salesman.

2. A radiation hazard exists in any fluoroscope. Correct usage requires adequate safety devices, proper calibration at regular intervals, operation only by trained individuals and strict adherence to an accurate exposure schedule. Supervision of such commercial machines is now vested chiefly among sales personnel who could not be expected to know their own limitations."

Evidence of the danger of cumulative doses of x-ray is constantly increasing. Proof of the usefulness of fluoroscopic examination shoe fitting is entirely lacking. In view of these two facts, pediatricians are justified in strongly advising parents to refuse to permit the use of these machines when buying shoes for their children.

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